THE ROLE OF CARBON DIOXIDE (AND INTRACELLULAR pH) IN THE PATHOMECHANISM OF SEVERAL MENTAL DISORDERS

ARE THE DISEASES OF CIVILIZATION CAUSED BY LEARNT BEHAVIOUR, NOT THE STRESS ITSELF?

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A SZÉNDIOXID (ÉS AZ INTRACELLULÁRIS pH) SZEREPE NÉHÁNY MENTÁLIS BETEGSÉG PATOMECHANIZMUSÁBAN
Nem maga a stressz, hanem tanult viselkedési formák okoznák a civilizációs betegségeket?

A széndioxid szerepe alábecsült a neuropszichiátriai betegségek patomechanizmusában, ugyanakkor fontos kapocs a lélek és a test között. A mindenkori lelki állapot többnyire a légzést is befolyásolja (lassítja, gyorsítja, irregulárissá teszi), ezért változik a pH. Másrészt a neuronok citoszoljának aktuális pH-ja a Ca^{2+} konduktivitás egyik legfontosabb modifikátora, ezért a légzés a Ca^{2+}-on keresztül közvetlenül, gyorsan, hatékonyan befolyásolja a "second messenger" rendszert. (A csökkenő CO_2 koncentráció mindig alkalózis, az emelkedő pedig acidózis irányában viszi el a pH-t, íly módon az előbbi gyorsít, növeli az arousalt, míg az utóbbi lassít, csökkenti az arousalt.) A H^+ ion koncentráció állandóságának megőrzése, helyreállítása az egyik legfontosabb homeosztatikus funkció, ezért a széndioxid szint megváltozása az ellenregulációs változások egész sorozatát indítja el. Mindazonáltal bizonyítható, hogy nincs tökéletes kompenzáció, ezért a kompenzáló mechanizmusok pszichoszomatikus betegségeket generálhatnak, minthogy másodlagos eltéréseket okoznak a "milieu interieur"-ban. A szerzők tárgyalják a CO_2 rendhagyó fizikókémiai tulajdonságait, a CO_2 és a katecholamin szintek összefonódó változásainak törvényszerűségeit (feedback), az akut és krónikus hipokapnia szerepét néhány hyperarousal kórképben (delirium, pánikbetegség, hiperventilációs szindróma, GAD, bipoláris betegség), a "locus minoris resistentiae" szerepét a pszichoszomatikus betegségek patomechanizmusában. Feltételezik, hogy a civilizációs betegségeket nem maga a stressz, hanem annak le nem reagálása okozza azáltal, hogy a CO_2 szint tartósan eltér a fiziológiástól. A növekvő agyi pCO_2, acidotikus citoszol pH, és/vagy emelkedett bazális citoszol Ca^{2+} koncentráció csökkenti a citoszolba történő Ca^{2+} beáramlást és az arousalt – dysthymiát, depressziót okozhatnak. Ez többnyire ATP hiánnyal és a citoszol Mg^{2+} tartalmának csökkenésével is jár. Ez az energetikai és ionkonstelláció jellemző az életkor emelkedésével korrelációt mutató krónikus szervi betegségekre is, és a legfontosabb kapcsolat az organikus betegségekkel, például az iszkémiás szívbetegséggel. A felvázolt modellbe beleillik, hogy egyes farmakológiai szerek (katecholaminok, szerotonin, litium, triacetiluridin, tiroxin), valamint az alvásmegvonás okozta H^+ és/vagy Ca^{2+} metabolizmus változás szintén a logikailag kívánt irányban hat.

KULCSSZAVAK: arousal, bipoláris betegség, civilizációs betegségek, delírium, depresszió, GAD, hyperventilációs szindróma, locus minoris resistentiae, milieu interieur, pánikbetegség, stressz, széndioxid, viselkedés

SUMMARY

The role of carbon dioxide (CO_2) is underestimated in the pathomechanism of neuropsychiatric disorders, though it is an important link between psyche and corpus. The actual spiritual status also influences respiration (we start breathing rarely, frequently, irregularly, etc.) causing pH alteration in the organism; on the other hand the actual cytosolic pH of neurons is one of the main modifiers of Ca^{2+}-conductance, hence breathing directly, quickly, and effectively influences the

second messenger system through Ca^{2+}-currents. (Decreasing pCO_2 turns pH into alkalic direction, augments psychic arousal, while increasing pCO_2 turns pH acidic, diminishes arousal.) One of the most important homeostatic function is to maintain or restore the permanence of H^+-concentration, hence the alteration of CO_2 level starts cascades of contraregulation. However it can be proved that there is no perfect compensation, therefore compensational mechanisms may generate psychosomatic disorders causing secondary alterations in the "milieu interieur". Authors discuss the special physico-chemical features of CO_2, the laws of interweaving alterations of pCO_2 and catecholamine levels (their feedback mechanism), the role of acute and chronic hypocapnia in several hyperarousal disorders (delirium, panic disorder, hyperventilation syndrome, generalized anxiety disorder, bipolar disorder), the role of "locus minoris resistentiae" in the pathomechanism of psychosomatic disorders. It is supposed that the diseases of civilization are caused not by the stress itself but the lack of human instinctive reaction to it, and this would cause long-lasting CO_2 alteration. Increased brain-pCO_2, acidic cytosol pH and/or increased basal cytosolic Ca^{2+} level diminish inward Ca^{2+}-current into cytosol, decrease arousal – they may cause dysthymia or depression. This state usually co-exists with ATP-deficiency and decreased cytosolic Mg^{2+} content. This energetical- and ion-constellation is also typical of ageing-associated and chronic organic disorders. It is the most important link between depression and organic disorders (e.g. coronary heart disease). The above-mentioned model is supported by the fact that H^+ and/or Ca^{2+} metabolism is affected by several drugs (catecholemines, serotonin, lithium, triaecetyluridine, thyroxine) and sleep deprivation, they act for the logically right direction.

KEYWORDS: arousal, behaviour, bipolar disorder, carbon dioxide, delirium, depression, diseases of civilization, generalized anxiety disorder, hyperventilation syndrome, locus minoris resistentiae, milieu interieur, panic disorder, stress

Introduction

The role of carbon dioxide is underestimated not only in the pathomechanism of somatic diseases but of mental disorders too (Gardner). It is a fact that the intracellular pH is strictly regulated in brain cells, and also marginal aberration of H^+ concentration may cause big functional deviation in neurons (Tombaugh & Somjen). The regulation of intracellular pH is complex, there are several compensational mechanisms (Boron). Carbon dioxide concentration is one of the most important factor which influences the intra- and extracellular pH. Why? CO_2 is extremely diffusible and in this way we can rapidly send or extract H^+ ions to or from all tissues, all cells (nearly the same time) drawing breath rarely or frequently. It is because CO_2 passes very quickly through the cellmembranes and it forms carbonic acid with H_2O which gives H^+ ions. On the other hand ions get slowly through membranes, even H^+-ion itself. That is because they have electric charge and become hydrated, and this multiplies their radius, but CO_2 does not have either of them and it is soluble in lipids (Sikter, 2007a). If we take our breath deeply or frequently our pulse speeds up proving that CO_2 has left the pacemaker cells of heart, and the alkalic cytoplasm allowes Ca^{2+} to enter in the cytosol. If we keep on this kind of breathing for a long time, our pulse will slowly come back to the incipient frequency because the organism compensates the alteration of pH in the cytosol. The lack of H^+ in cytosol increases conductance of Ca^{2+} and some other ions (Harvey et al.), thus it increases contraction, metabolism and O_2 requirement (Laffey et al.), and also increases excitability of neurons in the peripherium (Macefield et al.) and in the brain (Stenkamp et al.). All these events can be explained by the simple fact that lack of H^+ (=alkalosis) increases transmembrane conductance of ions and (consequently) increases active ion-pumping mechanisms too (because the original ion-status has to be restored). By contrast, acidosis decreases the transmembrane Ca^{2+}-conductance (Tombaugh & Somjen), decreases excitability of neurons, and the decreased Ca^{2+}-conductance can dramatically affect neurotransmitter release (Dodge et al..). In some cells the Ca^{2+} entry into cytosol itself increases cytosolic H^+ concentration, which physiological acidosis then limits further Ca^{2+} entry. (It is supposed to be a novel feedback mechanism:Tombaugh et al. 1998).

Alteration of carbon dioxide concentration can appear in the whole organism at the same time. If

it endures for a long time (several hours to one week), the organism starts to "compensate". Stability of extra- and intracellular pH is of high priority. Renal function and tissular buffer mechanisms (mostly) restore the pH in the cytosol of the cells and in the extracellular space, but the concentration of other ions is altered in the cytosol at the same time. The development of the new ionmilieu needs 5-7 days (Gennari et al.). The new ion-milieu of cells differs from the physiological one. (The restoration of original ionmilieu would need also 5-7 days at least.) Then chronic hypocapnia or hypercapnia is followed by cascades which alter the whole ionmileu in the cells, they may alter even the neurotransmitter/endocrine status (Dodge et al.). Therefore, it is inappropriate to call that process a "compensational mechanism", this name suggests that it is all right, while it is not! According to Claude Bernard alteration of milieu interieur can result in illness. It is very important that the new ionmilieu is similarly stable as the original one and it does not allow the organism to restore the original status. Therefore we should name this happening a „complication" (instead of "compensation").

The fact that intracellular pH is very strictly regulated does not mean it can not go wrong. Human is a species especially endangered by the long-term altereation of carbon dioxide level, we think. This is because he/she becomes hypo- or hypercapnic not only because of organic diseases, but of mental disorders too, and – most importantly — because of his/her behaviour! The last one is dangerous, because it may cause diseases of civilization. Why? It is frequently asserted that it is the "stress of life" itself that causes diseases of civilization (induced by "stress-hormones") (Selye). This statement might be wrong, because wild animals don't get diseases of civilization, even though they are at least as much stressed as human beings. In stress situations wild animals behave according to their instincts. The main behaviour is – according to Cannon – the "fight or flight" response, which is a hyperarousal condition (Cannon). The most important (according to our viewpoint) in this acute stress response is that in this condition there is a strong catecholamine (adrenaline, noradrenaline) rush and an acute hypocapnia as well. Wild animals during this hyperarousal condition will fight or flee, they take physical exercise, and this physical activity/muscle-work results in increased carbon dioxide production – this way they get a good chance to restore the decreased carbon dioxide level. Contrarily human acute stress response mostly differs from that because of their learnt behaviour. They mostly restrain their temper, the physical activity will fail and the hyperventilation/hypocapnia endures long causing a range of ion-movements through membranes and causing metabolic and endocrine alterations and illnesses because of the alteration of "milieu interieur". Namely, diseases of civilization are caused by the distress evoked by the lack of instinctive reaction to stress. Nowadays some researchers start to discover the theoretical significance of hyperventilation in stress induced illnesses (Schleifer et al.).

Several animals (e.g. opossum, newborn deer calves, some fish species, amphibians, reptiles, birds) react in another way to stress, they show "freezing behaviour" and "play dead". This hypoarousal condition brings slow breathing and bradycardia. Freezing behaviour is supposed to be caused (at least partly) by hypoventilation and hypercapnic acidosis. There is also a third model of wild animal reaction observed by Steen et al. in willow ptermigan hens (Steen et al.). In this case first the bird shows a freezing behaviour (but does not play dead) with hypoventilation, bradycardia, then after several minutes she starts to hyperventilate, and this way the hypoarousal condition converts to a very vigorous hyperarousal one. In this case a hypercapnic period is followed by a hypocapnic one, similarly to symptoms of human panic disorder (Sikter et al. 2007b).

The acute intentional hypocapnia (produced by voluntary hyperventilation) causes alkalosis in cells, because the compensational mechanism is much slower than the ventilation. This acute alkalosis fairly resembles to sympathicotonia (tachycardia, increased metabolism and O_2 requirement, increased Ca^{2+}-conductance, increased ion-pumping activities, etc.), although catacholamine level is normal or decreased (Sikter et al., 2007b). On the other hand the acute hypercapnia (acidosis) increases the output of catecholamines in the organism (Bailey et al.), e.g. in the locus coeruleus (Filosa et al.). In acute hypercapnia the catecholamine level is eleveted, although it seems to be parasympathicotonia. Why? According to Tenney there is a feedback mechanism beetween carbon dioxide level and catecholamine output of the organism (Tenney). In acidic condition catecholamine responsibility dramatically decreases, mean-

while catecholamine output increases, but in spite of this compensation acidosis makes sympathicotonia decrease (Kuijpers et al.). Contrarily, in alkalosis catecholamine responsibility and sympathicotonia increases (although catecholamine output slightly decreases) (Tenney, Schleifer et al., Sikter et al 2007b). Catecholamines, e.g. noradrenaline increase the Na^+/H^+ exchange in the cells (Smith et al.), that causes alkalosis in the cytosol, similarly to the effect of hypocapnia. We do not think it is a coincidence. It is evident that catecholamines take effect (at least partly) through causing intracellular alkalosis. Cannon's "fight or flight" response means a strong sympathicotonia/hyperarousal, because both catecholaminemia and hyperventilation cause alkalosis in the cytosol. "Freezing behaviour" causes parasympathicotonia/hypoarousal, because acidosis caused by hypoventilation is not totally compensated by increased catecholamine levels. In Steen's animal model hyperarousal appears at the end because the initial hypoventilation/hypercapnia generates heavy catecholamine output and then the cells/tissues become alkalic following hyperventilation. This ending is similar to Cannon's acute stress response but the pathomechanism is totally different. The final arousal might be higher in Steen's "biphasic" than in Cannon's "fight or flight" response animal model.

Locus minoris resistentiae

Organic diseases (e.g. organic pulmonary disorders as asthma bronchiale) often cause hyperarousal mental disorders too (Dratcu), on the other hand hyperarousal mental disorders often cause (or activate) asthma bronchiale which is thought to be sometimes purely psychogenic (Henderson). Why does a pathogenic substance (in our example: hyperventilation or hypophosphatemia induced by hypocapnia) cause different illnesses in different patients (Knochel), and why do different pathogenic substances cause (or worsen) illnesses on the same organ in a given patient? It may be explained with the theory of "locus minoris resistentiae" (LMR).

In case seriously harmful noxa affects the organism (e.g. hyperacute illness, cancer), it causes catabolism and degrades a part of (cells)-cytoplasm. In this case the (anabolic) reparation of tissues/cells cannot start until the harmful effect exists. If it stops, cells start to repair themselves, they start rebuilding cytoplasm, which consists of mainly amino acids and "cytoplasm building ions" (K^+, Mg^{2+}, Zn^{2+}, and inorganic phosphates) in strictly given proportions (Sikter, 2007a). Cells build-in the ions first into the cytoplasm with ATP energy (with pumping mechanisms). The available electrolytes in the extracellular space usually are not enough to supply "hungry" repairing cells – they struggle against each other for electrolytes. Those cells having worse metabolism and less ATP-content will lose fighting, they remain or become more and more ill. They are the LMR of an organism: they are the weakest link.

In case a weak harmful noxa affects the tissues/cells of the organism (e.g. moderate hypophosphatemia and alkalosis induced by hypocapnia), cells are able to repair themselves continously and fight against the damage. They restore their original ionmilieu, but not completely and not equally in the whole organism, the weakest cells/tissues get the worst of them, and they become ill, at first functionally, then organically (Sikter et al, 2007b). If they lose about $^2/_3$ of their ATP content, they may die. Cells may tolerate damage differently even in the same organ or same tissue by having different kinds of metabolism and different ATP energy contents. That statement is particularly important in organs containing electrically excitable cells (e.g. CNS or heart). That means certain cells will become functionally affected (and they start firing frequently or slowly) while other cells will not. This is why a noxious agent (like acute or chronic hypocapnia) can cause different mental, organic or psychosomatic disorders in different patients.

High arousal conditions

According to the second-messenger theory the neurotransmitters do not get into the cell, but send a "second-messenger" instead. Ca^{2+} is the classical second messenger (Rasmussen et al.). Very simply written: the amount of Ca^{2+} entering into the cytosol determines how strong is the response given by the neuron (e.g. during neurotransmitter release) (Dodge et al., Cooke et al.). Ca^{2+} enters the cytosol partly through the plasma membrane as a result of action potential, partly from the intracellular organelles (from sacroplasmic reticulums and mitochondria). The bigger the Ca^{2+} extracytosolic/intracytosolic (EC/IC) chemical potential is, the larger amount of Ca^{2+} will enter into the cytosol. That is why Ca^{2+} pumping mechanisms (which need ATP energy) have great im-

portance. The most important pumping mechanism is SERCA which pumps Ca^{2+} into the sarcoplasmatic reticulum (SR) and mitochondria: SERCA decreases the Ca^{2+} concentration of the cytosol, and thus allows more Ca^{2+} to re-enter. According to recent discoveries thyroxine acts through activating SERCA (Periasamy et al.). Decreased H^+ concentration (intracellular alkalosis, e.g. decreasing carbon dioxide concentartion in the case of acute hyperventilation) increases transmembrane Ca^{2+}conductance, thus increases the amount of Ca^{2+} entering into the cytosol (Tombaugh & Somjen). Catecholamines activate the Na^+/H^+ exchange mechanism, causing intracellular alkalosis as well. Therefore everything that decreases the concentration of intracellular (cytosolic) Ca^{2+} and/or H^+ concentration — in resting/basal state of cells — increases the Ca^{2+}-conductance in neurons and the excitability. H+ seems to be the most important ion which modifies Ca^{2+}-conductance, it can be considered a modifier of second messenger Ca^{2+}. E.g. intracellular alkalosis, acute hypocapnia, thyroxin and catecholamines increase arousal.

Delirium

It is very hard or impossible to differentiate between symptoms of delirium and those symptoms caused by severe hypophosphatemia in the central nervous system (CNS) (Knochel). Severe hypophosphatemia causes critically low ATP level in cells, especially in cells and organs of the "locus minoris resistentiae" of the organism (Sikter, 2007a). Delirium is observed to develop during incorrect refeeding after long-lasting starvation (Keys et al.). (Delirium is one of the symptoms of so called "refeeding syndrome".) Giving less minerals and more protein to malnurished, chronically starving patients, severe electrolyte deficiency can develop in the extracellular space too. Especially the hypophosphatemia is dangerous because it directly causes a lack of ATP in cells (see chemical equation: ADP+Pi= ATP), severe dysfunction or even cell death. Acute energy deficiency of the CNS can appear among symptoms of delirium. (But patients did not drink alcohol at all.)

Delirium in "refeeding syndrome" is the key to other types of delirium. After chronic alcohol abuse delirium tremens frequently develops after alcohol withdrawal. Chronic exposure to alcohol causes persistent toxic damage to cells of the organism in case of chronic alcoholism, but it maintains a pathological balance. After abrupt withdrawal of alcohol the balance falls over. The cells of the organism start to regenerate but there is insufficient material for building up the cytoplasm, especially the "cytoplasm building minerals" are missing. Developing hypophosphatemia can cause acute energy deficiency mainly in the CNS, because hyperventilation, hypocapnia (which is an obligatory symptom of delirium tremens) (Victor) decreases cerebral circulation, O_2 supply and on the other hand it increases energy demand and causes high arousal. Flink pointed out that alcohol abuse causes negative magnesium balance, and contrary after alcohol withdrawal the magnesium balance becomes positive (Flink), meanwhile hypomagnesemia, hypokalemia, hypophosphaetemia often develop accompanying hyperventilation. Although only a few researchers recognized the connection between hypophosphatemia and delirium tremens (Funabiki et al.), that is because serum Pi test is not a routine examination. However incidence of hypophosphatemia is 30-50% among hospitalized alcoholics. Othervise hyperventilation itself causes hypophosphatemia too, it is the most common cause of hypophosphatemia in hospitalized patients (Ratkovic-Gusic et al.). There is an inverse correlation between pCO_2 level and hyperarousal symptoms of CNS during alcohol withdrawal (Victor), that hyperventilation plays an important role in the pathomechanism of delirium tremens. Hyperventilation and anxiety are part of subacute alcohol withdrawal syndrome too (Roelofs et al.), and probably play a decisive role in craving for alcohol and in the relapses. It may be a strategy to precede hyperventilation periods after alcohol withdrawal and in this way to precede hyperarousal and craving for alcohol. Patients know from their experience that drinking of alcohol abolishes symptoms of hyperarousal and craving. (That is because alcohol restores previous pathological balance of the organism – see above).

Delirium often occurs in demented patients. We suppose that the pathomechanism of delirium developing in demented patients is similar to the above-mentioned. We did not find any data either in relation to hypophosphatemia or hyperventilation, although Miyamoto et al. created an animal model of "postoperative delirium in elderly" (Miyamoto et al.). Postoperative delirium develops in that groups of elderly patients, in it might occur spontaneously too. It is supposed that these two pathomechanisms are similar. Precondition of de-

veloping delirium is pre-existing brain damage or significant cerebrovascular insufficiency. Damaged, sick cells usually have a lower resting membrane voltage potencial, the threshold potential gets closer to resting potential (Sikter, 2007a), that is why the damaged cells are often more excitable. Hyperventilation/hypocapnia plays an essential role in the cases of postoperative delirium under mechanical ventilation. Patients that are mechanically hyperventilated keep on overbreathing for a while even after the operation, that is why they go into delirium. Hypocapnia further decreases cerebral circulation meanwhile it increases O_2 demand and causes hyperarousal. Levkoff et al. analysed delirium among elderly hospitalized patients, 34% of patients experienced individual symptoms of delirium without meeting full criteria, 31,3% developed new-onset delirium. About 80% of patients had residual cognitive impairment even 6 months later (Levkoff et al). These data suggest that delirium is a common disorder that may be substantially less transient than currently believed and that incomplete manifestations of the syndrome may be frequent. Delirium developing after hospitalization might be caused by Cannon's "fight or flight' response, because patients having damaged brain did not perceive the situation properly and they suppose to be in danger. Feeling horror they can release enormous amount of catecholamines and start hyperventilating. We suppose that a vicious circle develops in the cases of spontaneously evolving delirium in elderly. Patients with damaged brain tend to get involved in hyperventilation and delirium – frequent delirium causes hypoperfusion of brain and harms it, causing more brain damage, etc.

Therefore delirium evolves if the brain is damaged (functionally or structurally too), suddenly a disproportion develops between supply and demand of ATP energy and of "cytoplasm building minerals" (because of developing hypophosphatemia, hypomagnesemia, etc.) Hyperventilation is an obligatory part of delirium: it increases metabolism, O_2 demand, causes high arousal, and at the same time it causes hypoperfusion in the brain.

Panic disorder

Although panic disorder (PD) seems to be a typical hyperarousal condition, not only the pathogenetic role of hyperventilation, but even its existence was denied by many researchers for a long time. The minority of authors now think that hyperventilation would have a significant role in the pathomechanism of panic disorder (Lum, Ley). That is because the carbon dioxide challenge test is widely used to provoke panic (Griez), but voluntary hyperventilation is only a weak challenger (Nardi et al.). We made an attempt to integrate the three main theories (Sikter et al., 2007b. See the full text article: http://www. scielo.br/pdf/rbp/v29n4/a15v29n4.pdf) about the relationship between hyperventilation and panic disorder, even though according to Wilhelm et al. (2001a), these theories would include antagonistic contradictions. The three statements are: A/ hyperventilation is a protective/preventive mechanism against panic attacks; B/ it is a physiological response to hypercapnia; C/ it can induce panic attacks.

We think that panic attack is a cascade of events where hyperventilation has different roles in different times. Chronic hyperventilation is probably a precondition of (respiratory subtype) panic attack, although it defends against panic. While it exsists, spontaneous panic attacks cannot arise (see statement A). Chronic hyperventilation can be generated by either organic diseases (e.g. asthma bronchiale) or mental conditions (e.g. sighing or crying for a tragedy). Compensational mechanisms set off metabolic acidosis that neurtralizes hyperventilational alkalosis, this compensational process lasts at least for a week. In the state of compensated hypocapnic alkalosis extra- and intracellular pH stays in the normal range. The depressed pCO_2 level starts to go up to the normal level (or slightly higher) before the attack. The elevating carbon dioxide promptly diffuses into cells and causes acidosis, which increases catecholamine release from different cells (e.g. noradrenaline release from locus coeruleus) (Filosa et al.). On the other hand, elevating carbon dioxide level also evokes acute hyperventilation (through a brainstem reflex), which may be more vigorous than previously. (see statement B). At this point hypercatecholaminemia (induced by previous acidosis) and alkalosis (abruptly decreasing pCO_2 level) evolve at the same time. Alkalosis multiplies CNS-responsiveness to catecholamine levels, and it lasts for several minutes to break down catecholemines. This coexistence means an intense sympathicotonia, a very high arousal. (The cascade of events is similar to Steen's animal model – a hypercapnic period is followed by a hypocapnic one) (Steen et al.). High catecholamine level/sympathicotonia can provoke panic attacks (Cameron et al.). Panic at-

tack is precipitated by this second (acute) hypocapnia (see statement C) plus catecholaminemia induced by previous acidosis.

We have illustrated panic attack on a theoretical diagram. According to this panic theory intra- and extracellular pH is thoroughly compensated before the attack, but the acidosis would be overcompensated by acute hypocapnic alkalosis during the attack. The main problem is that the different compensational mechanisms work out at different rates. Carbon dioxide level can change in the whole organism in a few seconds, the elimination of catecholamines lasts for several minutes, and the clearing of blood from metabolic ("titratable") acidity takes at least one week. This is one of the many reasons there is no perfect compensational mechanism.

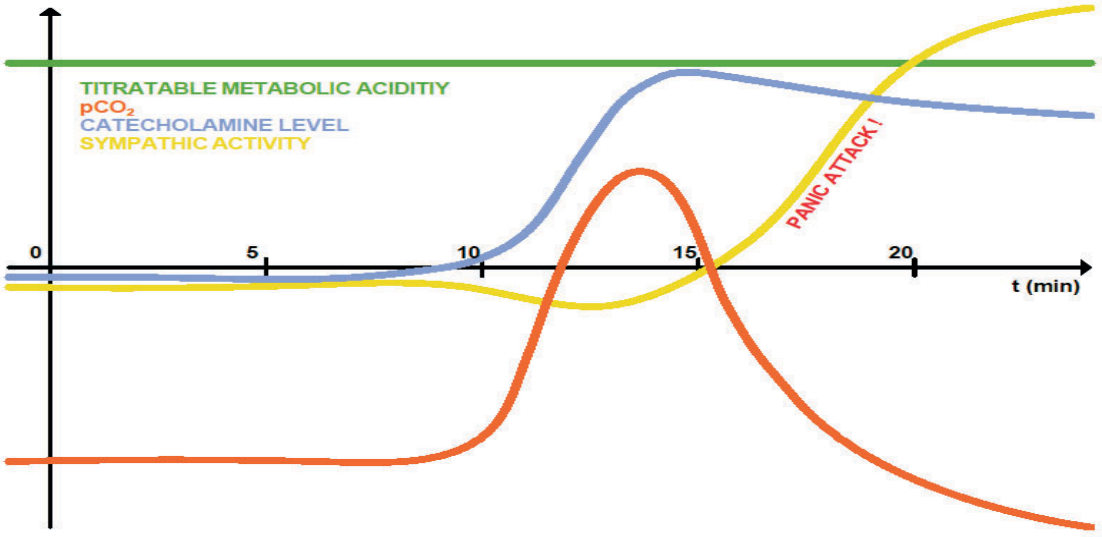
Hyperventilation syndrome, GAD

Somatic symptoms of hyperventilation syndrome are similar to those of panic disorder, except for the panic attack itself (Cowley et al.). Acute and chronic hyperventilation may cause alterations and symptoms in almost any organs, not only in the CNS (Gardner, Laffey et al.).

GAD (generalized anxiety disorder) is pathogenetically also like PD, but with important differences. pCO_2 level shows great variability in PD (mainly in the hypocapnic range), but it seems to be around the normal level in case of GAD patients (Wilhelm et al. 2001b). Respiration is extremely unstable and irregular in PD. Respiration variability in GAD is lower than in PD, though it is higher than physiologically. Alteration of pCO_2 level makes catecholamine levels fluctuate because of altering pH. Actual catecholamine levels interfere with actual pCO_2 levels, which results in arousal alterations (like PD). Namely both pCO_2 and catecholamine levels are fluctuating but with different rates – their effects on arousal sometimes added together, sometimes substructed. Another mechanism which intensifies alteration of arousal: changes of carbon dioxide and catecholamine level may affect on most neurons similarly. Neurons in the brain are working together. Those neurons linked to each other in a row are able to multiply both hypo- and hyperarousal.

We suppose there is a fluctuating pCO_2 level slightly around the normal values at GAD patients. Intracellular pCO_2/pH and catecholamine level would keep changing permanently, causing more

Fig. 1. Schematic diagram of (respiratory subtype) panic attack



PERIOD A/ (preconditional situation): chronic hypocapnic alkalosis is compensated by chronic metabolic acidosis (pH is in normal range). Arousal is normal.
PERIOD B/ pCO_2 level starts to normalize (is elevating): intracellular acidosis arises, catecholamine output increases. Arousal is normal or decreased.
PERIOD C/ pCO_2 level reflexively decreases, responsibility of neurones to catecholamines increases, catecholamine level is still high – panic attack may arise.
(PERIOD D/ Feeling and fearing of somatic sensation may elevate catecholamine level and slows down panic attack relief.)
(Veltman et al.) (Period D is not on the diagram!)

or less arousal than in the healthy controls. That is why arousal fluctuates permanently, even dysthymia can arise (Pini et al.). If this statement is right, we could call GAD "bipolar anxiety" too. We think that every hyperarousal condition involves hypoarousal periods too. One of the reasons for this may be that pH elevation (and pCO_2 decrease) has to be corrected from time to time. (Cytosolic pH is limited in a narrow range even in pathological conditions.)

Both alkalosis and acidosis increases cytosolic Ca^{2+} in the cells. While acidosis increases basal cytosolic Ca^{2+} level (Bers et al.), alkalosis increases inward Ca^{2+}-current. This Ca^{2+} overload requires more pumping activity and ATP energy — the energy supply may become insufficient after a long-lasting alkalosis. Therefore basal cytosolic Ca^{2+} may rise even in resting state in hyperarousal conditions too. That is why GAD increases the risk of coronary heart disease even in the absence of major depressive disorder (Barger et al.), and GAD can turn into depression, we think. SSRIs may be effective in PD and in GAD because of increased basal cytosolic Ca^{2+} level. It is evident that cytosolic Mg-ATP complex and Mg^{2+} itself often decrease, which are inseparable from elevated cytosolic Ca^{2+} level – in hyperarousal disorders, too (Durlach et al., Barbagallo et al., Bobkowski et al., Sikter 2007a).

GAD means permanently fluctuating ventilation and altering arousal, which hypo- and hyperarousal conditions affect each other and may cause vicious circles through psychogenic mechanisms. This fluent alteration may result in depression and/or psychosomatic disorders. Being human we have to behave ourselves, and our activities often separate from stress-induced hyperarousal. It seems plausible that doing physical execises frequently would be preventive or curative on the harmful effects of stress. EITHER we can learn how we could control our breathing to maintain euventilation, and this way the milieu interieur of cells/tissues, OR we can try to restore the ion-alterations in tissues by giving special electrolyte mixtures (this issue needs further research). AND/OR: It is also a curative process to break psychogenic vicious circles off (e.g. by psychotherapy).

Bipolar disorder

Mood and anxiety disorders appear in different brain structures, thus it is possible that the same pathomechanisms take place in both kinds of disorders. (See LMR.) It is proved that intracellular pH is one of the most important factors influencing inward Ca^{2+}-current in hippocampal neurons too (Tombaugh & Somjen, Tombaugh 2008). There is frequent (20-60%) comorbidity between bipolar disorder (BD) and PD (MacKinnon et al. 2006) and both have episodic courses. MacKinnon et al. (2009) found heightened anxiety responses among BD patients during CO_2 challange test, which is somewhat similar to PD patients' answer, but BD patients were not examined whether they would have been chronically hyperventilating or not. Anyway it is possible that hyperventilation/hypocapnia plays a role in the pathomechanism of BD too.

It is an important similarity of both of these disorders, that particular regions of the brain have elevated lactate levels (Dager et al.). This may be the key to solve the problem. Dager et al. investigated miscellaneous intermadiate chemical matters with a special "PEPSI" technique in the hippocampus of medication-free BD patients. They only found the lactate to be significantly elevated in both types of BD patients. (BDI patients had higher level lactate than BDII.) Lactate level was much higher in the gray matter signalling where it arose. Elevated lactate level usually coexists with hypocapnia in the brain, but it is not often clear which of them is the cause and the consequence. It is an important fact that lactate arises in cells only in alkalic conditions (Maddock), then it diffuses into the extracellular space causing acidosis. Only the quickly spreading hypocapnic alkalosis is able to keep step with the also diffusible lactate. They can compensate each other. Perhaps the pH is not homogeneous in all neurons' cytosol. There may be a certain "pH-mosaicism" in neurons, because lactate-CO_2 equilibrium might not be perfect, on the the other hand the places of lactate production and utilisation might be separated. We think that certain neurons of the hippocampus should be alkalic in medication-free BD patients, other neurons might have acidic cytosol. "Alternating carbon dioxide level theory" would be suitable to explain the episodic courses of BD. Although this is merely a hypothesis because there are no direct data for the coexistence of hyperventilation and BD, intracellular metabolic alkalosis may be an alternative pathomechanism to increase Ca^{2+}-conductance and/or to produce lactate, e.g. by improper ion-pumping mechanisms (Boron).

There is a growing amount of data showing that BD is a genetically determined disorder, and the main alteration would be in mitochondria (Konradi et al.). Energetic insufficiency may only be a consequence because ATP deficiency cannot cause hyperfunction, we think. According to an animal model there seems to be an increased Ca^{2+}- conductance from the mitochondria membrane to cytosol (Kubota et al.). The hyperactive Ca^{2+} dynamics is proved in B lymphoblasts from BDI patients (Perova et al.). It is unknown what kind of mechanism increases Ca^{2+}-conductance in mitochondria. It might be a genetic failure which would cause alkalosis in the cytosol or in mitochondria by pumping mechanism (Boron), but non of the researchers found intracellular alkalosis in the limbic system. (Perhaps recent methods are not sensitive enough, and the existing lactic acidosis of brain might be disturbing as well.) Kato et al. found neutral pH during ^{31}P-MRS technique in the medication-free manic period, which turned acidic after lithium treatment, while patients became euthymic. We can construate a BD model, if we accept Kato's statements. (Although others could not verify Kato's results.)

According to this model: BD is caused by an increase (of unknown origin) of Ca^{2+}-conductance in mitochondrial membranes. The increased inward Ca2+-current makes SERCA work harder (to restore the original cytosolic milieu), that needs more ATP energy. Therapeutically given lithium acidifies the neurons' cytosol and Ca^{2+}-conductance becomes normal. In this hypothetical model the intermittent hypocapnia/hyperventilation would play only an episodic role in episodic courses. It is known that lithium affects acid-base metabolism (Kraut et al.). It is not known how lithium acidifies the cytosol, one of its intracellular acidifying mechanism may be inhibiting the Na^+:HCO_3 cotransporter (Amlal et al.). It is likely that the primer event is that lithium inhibits H^+-ATP-ase activity, at least in rats' renal collecting duct cells (Kim et al.). A similar blocking action of lithium on limbic system neurones would be fitting well into our model. Maybe that is why lithium attenuates intracellular calcium mobilization.

We note that there are some similarities between hyperthyreodism and BD. Although in hyperthyreoidism the primer event is the activation of SERCA, increased inward Ca^{2+}-current is only its cosenquence. Nevertheless treating hyperthyreoidism with lithium is a reliable and quick method to restore proper inward Ca^{2+}-current and metabolism (Akin et al.). We suppose rapid cycling courses are caused by pCO_2 level changes. Stable, deep depression may arise after energetical insufficiency, when SERCA cannot restore basal cytosolic Ca^{2+} level due to the lack of ATP.

Low arousal conditions

As mentioned above, the hyperarousal conditions are often followed by hypoarousal ones. Moderate forms of "hypoarousal anxiety" usually are considered to be normal, while we may call its definite form "neurotic depression" or dysthymia. Dysthymia is lighter and more fluctuating than depression.

ATP-content of cells decreases with ageing and illnesses (Barbagallo et al., Sikter 2007a,). Cells/neurons struggle against equilibration of ions in their whole life, namely to maintain their chemical potential between the extra- and intracytosolic spaces. Though the chemical potential of Ca^{2+}EC/Ca^{2+}IC, Na^+EC/Na^+IC, H^+EC/H^+IC and of Mg^{2+}IC/Mg^{2+}EC, K^+IC/K^+EC decreases parallel with ATP-content. When intracytosolic Ca^{2+}-content increases, responsibility of neurons decreases, because Ca^{2+}-conductivity decreases. Contrarily when the chemical potential of Na^+ and/or K^+ decreases, responsibility/excitability of neurons increases because the membrane potential usually also decreases and gets closer to threshold potential, that is why (electrical) stimulation excites neurons easier then formerly. According to these alterations the structure of arousal alters with ageing. The incidence of GAD, PD and manic periods of BD decreases while that of depression and other hypoarousal conditions increases because of the elevated cytosolic Ca^{2+} level. Although the hypocapnic alkalosis is common in the elderly because of cardiovascular and other organic disorders, delirium is the only hyperarousal condition which occurs more often with ageing. Electrically excitable cells having higher resting/basal Ca^{2+} concentration react less to hypocapnic alkalosis, but if the membrane potential decreases, neurons become irritable again. We think that the elevated basal cytosolic Ca^{2+}-content is why depressed patients show less heart rate variability and altered autonomic nervous system activity (Carney et al.). Elevated basal cytosolic Ca^{2+}, decreased Mg^{2+} are the missing links which may join several endemic, ageing-associated disorders together (Barbagallo

et al., Sikter 2007a.). This altered ionmilieu may be the most important link between depression and coronary heart disease too. The cytosolic Ca^{2+} accumulation-tendency (with ageing and illnesses) refers to the whole organism. (Memento: All of the cells have to struggle against the equilibration of ions between extra- and intracytosolic space.) The ionic equilibration-tendency though is not homogenous in the whole organism because of the LMR phenomenon and contraregulation of endocrine system (Sikter 2007a). The hypothesis of elevated basal cytosolic Ca^{2+} level in limbic system neurones is an early depression theory (Dubovsky et al.). Cytosolic H^+ concentration rising tendency is similarly common with ageing and illnesses due to erroneous H^+-pumping mechanisms. Several mechanisms lead to intracellular acidosis, the lack of ATP is one of the most important (Sikter 2007a). Bioenergetic insufficiency (the lack of ATP) may cause cytosolic Ca^{2+} accumulation and Mg^{2+} deficiency as well. This state frequently occurs in depression, furthermore it may be the cause of depression. Therapeutically given thyroxine may restore ATP level and improve depression (Iosifescu et al.).

Depression

According to our hypothesis, there are three ways for the cytosolic ionmilieu of limbic system neurons to become hypoaroused, and depression arise. We suppose that a very high basal cytosolic Ca^{2+} level exists in major depressive disorder, which is partly genetically determined. On the other hand plenty of organic disorders occur with increased intracellular Ca^{2+}-content, though we don't know exactly which genetic-endocrine constellation elevates the cytosolic Ca^{2+} content of mainly the limbic system.

Elevating carbon dioxide concentration certainly causes acidosis in the cells, because compensatory mechanisms follow carbon dioxide alterations slowly. pCO_2 is usually elevated in obstructive sleep apnea (OSA) syndrome, and it is elevating during the sleep. Perhaps that is why the incidence of depression is about 50% in this disease. Symptoms of depression practically disappear after continuous positive airway pressure treatment (CPAP) (Schwartz et al.). Unfortunately, hypoxia also coexists in OSA, that is why we do not know whether hypercapnia (acidosis) or hypoxia is the actual cause of the depressive symptoms. Depressive symptoms were also present in 40-60% of the cases of COPD (de Voogd et al.) (but anxiety was similarly common). Although depression played a significant role in mortality, there was no correlation between elevated CO_2 level and depressive symptoms. (Elevated CO_2 level does not necessarily mean also elevated H^+ ion level in cytosol, because of compensatory mechanisms.) In the cases when COPD patients were given O_2-therapy, they fell into serious depression, or their existing depression worsened (Maurer et al.). It is understood that O_2-therapy is elevating carbon dioxide level, so it is evident that elevating carbon dioxide level itself (the acidic pH in neurons' cytosol) is what causes the depressive symptoms, not hypoxia. Sleep deprivation is a useful therapeutic option in the treatment of depressive disorders (Svestka et al.). Carbon dioxide level is elevating also in physiological sleep, mainly in the NREM periods (Casey et al.). Partial deprivation of REM-sleep may be also (but less) effective in depression, perhaps because pharynx muscles relax exaggeratedly during REM periods (in pathological conditions) causing hypoxia and hypercapnia in OSA.

We can influence the cytosolic H^+ and/or Ca^{2+} milieu of the neurons in the limbic system giving drugs that are effective against depression. Noradrenaline decreases H^+ concentration in rat hippocampus CA1 cells due to activating Na^+/H^+ exchange mechanism (Smith et al.). Triacetyluridine (TAU) is a less notorious drug curing depression, although Jensen et al. found that TAU decreased depressive symptoms and increased brain-pH in BD patients (Jensen et al.). SSRIs are elevating serotonin level on their receptors. Serotonin also has a positive inotropic response on rat cardiomyocytes, increases SR Ca^{2+} content, and cytosolic inward Ca^{2+} current. (Birkeland et al., authors do not know which is the primer event, while basal cytosolic Ca^{2+} level was not examined.)(Birkeland et al.) This effect of serotonin on Ca^{2+}-movement fits well into our depression-model, although it may not be a primary event but a consequence of decreasing cytosolic H^+-concentration. It was found that serotonin alkalinized both crypt and villus cells of rabbit ileum via inhibiting Cl^-/HCO_3-exchange and/ or stimulating Na^+/H^+ exchange (Sundaram et al.).

As we saw, hyperarousal conditions are usually followed by hypoarousal conditions (GAD–dysthymia, hyperarousal delirium–hypoarousal delirium, mania–depression, etc.) The only stable arousal condition is major depressive disorder. That is

why we can call it unipolar depression. That is because we can easily drop from a high peak (hyperarousal), but it is hard to climb up from a deep pit (depression) – the low energetic conditions are stable. (Is it because the second law of thermodynamics?) Unipolar depression is an entity, but there are plenty of similar conditions. Most of the serious ageing-associated disorders have a high coincidence with depression (e.g. CNS organic disorders, cardiovascular disorders, pulmonary disorders, uremia, cancer, malnutrition, etc), perhaps because of increased basal cytosolic Ca^{2+} and/or H^{+} concentration (Barbagallo et al., Sikter 2007a).

It is important (both theoretically and practically) that we can mobilize ATP energy and decrease basal cytosolic Ca^{2+} level by giving thyroxine and activating SERCA in a part of depressive cases, even if hypothyroidism is not evident, in this way we can cure depression (Iosifescu et al.).

ABBREVIATIONS
ATP=Adenosine TriPhosphate
BD=Bipolar Disorder
BDI=Bipolar Disorder type I
BDII=Bipolar Disorder type II
CHD=coronary heart disease
CNS=central nervous system
CPAP=Continuous Positive Airway Pressure
COPD=Chronic Obstructive Pulmonary Disease
GAD=Generalized Anxiety Disoorder
EC=ExtraCytosolic (SR and mitochondria are intracellular but extracytolosic!)
IC=IntraCytosolic
LMR=locus minoris resistentiae
NREM=Non-Rapid Eye Movement
pCO_2=partial Pressure of Carbon Dioxide
Pi= inorganic phosphate
PD=Panic Disorder
REM=Rapid Eye Movement
OSA=Obstructive Sleep Apnea
SERCA=Sarcoplasmatic Reticulum Ca2+-ATP-ase
SR=Sarcoplasmatic Reticulum
SSRI=Selective Serotonin Reuptake Inhibitor
TAU=TriAcetylUridine

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Felhívás

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