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Hypocapnic hypothesis of Leigh disease

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ABSTRACT

Leigh syndrome (LS) is a neurogenetic disorder of children caused by mutations in at least 75 genes which impair mitochondrial bioenergetics. The changes have typical localization in basal ganglia and brainstem, and typical histological picture of spongiform appearance, vascular proliferation and gliosis. ATP deprivation, free radicals and lactate accumulation are suspected to be the causes.

Hypocapnic hypothesis proposed in the paper questions the energy deprivation as the mechanism of LS. We assume that the primary harmful factor is hypocapnia (decrease in pCO_2) and respiratory alkalosis (increase in pH) due to hyperventilation, permanent or in response to stress. Inside mitochondria, the pH signal of high pH/low bicarbonate ion (HCO_3^-) is transmitted by soluble adenyl cyclase (sAC) through cAMP dependent manner. The process can initiate brain lesions (necrosis, apoptosis, hypervascularity) in OXPHOS deficient cells residing at the LS area of the brain. The major message of the article is that it is not the ATP depletion but intracellular alkalization (and/or hyperoxia?) which seem to be the cause of LS.

The paper includes suggestions concerning the methodology for further research on the LS mechanism and for therapeutic strategy.

Introduction

In 1951 a British neuropathologist found at an autopsy in an infant, who had died after a rapid disorder of an unknown cause, the brain lesions of localization and morphology not previously specified [1]. Dr. Denis Leigh thoroughly described the brain changes which soon turned out to be a new neuropathological entity (named after him). Within a relatively short period of time several dozen of similar cases were found [2], still without the exact knowledge concerning the cause of the disease. In the meantime, the neuropathological diagnosis, possible exclusively *post mortem*, was successfully replaced by magnetic resonance imaging (MRI) of the brain [3], which allowed effective diagnosis of Leigh syndrome (LS) in live patients.

A disorder of mitochondrial bioenergetics (oxidative phosphorylation, OXPHOS) was initially assumed as the biochemical basis of LS, which could not have been effectively confirmed until the 1990s, when the first mutations in genes related to OXPHOS were identified in LS patients [4]. To date, at least 75 monogenic defects impairing OXPHOS (isolated complex I and IV, compound defects, other) resulting in LS development, have been described [5].

Acute onset of LS occurs after a latency period. Subsequent stepwise progression of neurologic decline is typical [6,7]. Respiratory impairment (bradypnea, hypopnea, episodes of apnea) is commonly described in LS and is attributed to brain stem involvement [8]. The major biochemical finding has been the increase in lactate concentration in urine, plasma, cerebrospinal fluid and brain tissue [6].

Macroscopy examination of the brain shows focal symmetric necrotic lesions of various intensity in thalamus, basal ganglia, mesencephalon, pons, medulla oblongata, certain parts of cerebellum (pedunculi) and spinal cord (posterior fasciculi). Light microscopy of the affected areas reveals: spongiform appearance, vascular proliferation, demyelination and gliosis; neurons are relatively spared [1,9]. The mechanism of the development of such lesions is extensively studied with focus on a deprivation of cellular energy (ATP), free radicals overproduction, acidosis, lactate- and excitotoxicity [9] without final conclusive results. A number of experimental models of LS were applied for the research [10–12].

The conception of "hypocapnic hypothesis of LS" was established on the basis of our long-term observations of over a hundred infant patients with LS caused by SURF1 mutation [13], hospitalized in the metabolic and intensive wards. In those patients, if observed at the very onset, we detected the hyperventilation episodes (sighing, facial expression of fear) associated with acid-base status indicated hypocapnic alkalosis [14–16].

Recently, an argument pro "hypocapnic hypothesis" have come from an independent study [17–19]. The team of Mootha reported a dramatic effect of hypoxia in preventing LS in a mouse model

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[17]. Since hypoxia usually occurs with carbon dioxide accumulation, the opposite to the carbon dioxide loss (hypocapnia), our "hypocapnic hypothesis" might help to explain the mechanism of reported beneficial consequence of hypoxia on the course of LS [17].

Hypocapnic hypothesis of Leigh syndrome

Details of the hypothesis

Hypocapnic hypothesis of LS assumes that, for the OXPHOS deficient brain cells, the primary harmful factor in triggering this condition is decrease in pCO_2 (hypocapnia) associated with increase in pH (alkalization) occurring during hyperventilation, permanent or stress-related, and not energy deprivation. The pH signal inside mitochondria is transmitted by soluble adenyl cyclase (sAC) in cAMP dependent manner to initiate brain lesions (necrosis, apoptosis, hypervascularity). The effect is limited to the brain cells with OXPHOS deficiency residing in the area corresponding to LS.

Evaluation of the hypothesis

Respiratory alkalosis

Internal acid-base homeostasis is fundamental for maintaining life [20,21].

Transport of gases from respiratory air to pulmonary alveoli and blood through biological membranes is not limited by the necessity of operation of ionic transporters. Gaseous CO_2 moves freely in the body fluids and penetrates extra- and intracellular compartments in order to equalize partial pressure. During intense breathing, the equilibrium of CO_2/HCO_3^-/pH is adjusted to the changes in carbon dioxide pressure without significant energy expenditure.

Inside cell compartments, partial pressure of CO_2 (pCO_2) causes CO_2 solubility and carbonic acid formation ($CO_2 + H_2O = H_2CO_3 = -H^+ + HCO_3^-$). The pH value is automatically adjusted with intracellular acidification (in high pCO_2) or alkalization (in low pCO_2). The membranes are not permeable for ions (HCO_3^-, H^+), so the exchange of H^+ is not longer possible between adjacent compartments of the cell. The acid-base status in the compartment has to be subjected to a local biochemical buffering.

Hyperventilation caused by hypoxia improves oxygenation (increase in pO_2) and abolishes oxygen demand. The hyperventilation always coexists with parallel exhalation of CO_2 causing hypocapnic alkalosis. In physiological conditions, the hypocapnia stops hyperventilation through inhibition of respiratory centre. Hypopnea restores the previous $pH/pCO_2/HCO_3^-$ equilibrium. In stress-related hyperventilation, the inhibition of respiratory centre may by less pronounced and hypocapnic alkalosis lasts longer.

Respiratory alkalosis is rarely observed in humans. Acute episodes occur e.g. in hysteria, sepsis, head traumas, neonatal hyperammonemia. The hyperventilation test is used in neurology to evoke epileptic EEG changes.

Chronic respiratory alkalosis (with blood pH > 7.45) is known from the studies conducted at high altitude, and during long distance migrations of birds.

Deleterious effect of hypocapnic alkalosis on the brain has been evidenced by a number of empirical data and experimental studies. Severe hypocapnia correlates with poor expectations (death, major disability) for children patients who suffered from major head injuries [22]. Furthermore, it causes changes in SEPs in hyperventilated neurosurgical patients [23], or attenuated vasodilatatory effect of N_2O in hyperventilated healthy adult volunteers [24].

Cerebral vasoconstriction and reduced cerebral O_2 supply occur in birds during high-altitude flights [25]. Systemic hypocapnia in mechanically ventilated rabbits leads to decrease of vascular blood flow, reduction of tissue oxygenation and decrease removal of acid metabolites [26].

Respiratory alkalosis is a physiological cause of the increase of lactate concentration in the body fluids. It inhibits several glycolytic and gluconeogenetic enzymes, which leads to lactate accumulation [27–29]. This phenomenon was clearly shown in experiments on animals [30]. However, it is poorly known and happens to be neglected in the clinical practice and research [31].

Soluble adenyl cyclase

Soluble adenyl cyclase (sAC) is a new type of adenyl cyclases, the enzymes generating cAMP – the second messenger [32], whose role might prove more important with future research. In contrast to well-known membrane-bound adenyl cyclases, the sAC is not activated by hormones, but is directly modulated by concentration of HCO_3^- inside the cells and intracellular compartments (Fig. 1). The discovery of sAC revealed that the physiological acid-base status (pCO_2/HCO_3^-/pH) can be sensed via cAMP signaling. This CO_2/HCO_3^-/pH chemosensor mechanism is evolutionarily conserved and is involved in a wide variety of physiological systems [32,33]. The pathogenic significance of the sAC discovery is still fragmentary and the proper research methodology is extremely difficult to apply [32].

The sAC expresses its action selectively inside intracellular structures such as mitochondria [34]. The sAC is highly expressed in astrocytes, which probably protects neurons from glucose shortage by providing lactates [35]. Interestingly, a functional specialization of astrocytes occurs defined by their localization [36]. Astrocytes residing in the chemosensitive area of the brainstem (which is impaired in LS) can sense pH and react with changes in ATP release.

An evidence for the relationship between mitochondrial energetic pathways and pH may be derived from the study on pH influence on general (48 genes) transcriptomic modifications in corals [37]. It showed opposite up- and down-regulations of OXPHOS and apoptosis related genes under higher and lower pH conditions of the surrounding water. Translational value of these findings for human pathology is entitled by strongly conserved structure of sAC as a pH sensor. In fact, the changes sensitive to agonal-pH state were reported for mitochondrial-related gene expression [38].

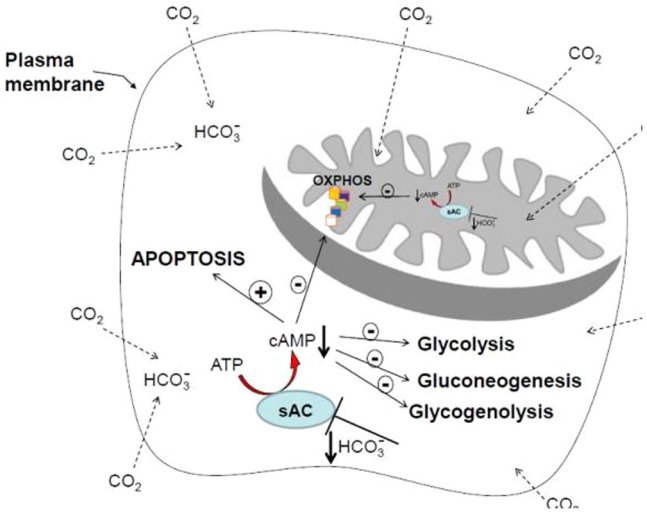

Fig. 1. Scheme of adenyl cyclase regulation in mitochondria.