Malnutrition and experimental epilepsy


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ABSTRACT

Introduction: Disturbances in intrauterine environment can have harmful effects on the fetus and pathological consequences persisting throughout adolescence and adulthood. Protein restriction during the prenatal period has a significant impact on growth and development of the central nervous system. Food restriction increases the risk of neurological disorders such as epilepsy. Objective: To relate the programming model by malnutrition and its implications in experimental epilepsy. Material and methods: There has been research papers published in the databases Medline, PubMed, CAPES journals, ScienceDirect and Scielo. The keywords selected for the study included epilepsy, Status Epilepticus, pilocarpine, malnutrition, programming. Results and discussion: Several studies in animal models or humans highlights the possible adverse effects of malnutrition at the onset of epileptic seizures. The vulnerability immunological, biochemical and electrolyte abnormalities and hypoglycemia may be the factors responsible for the intensification of the epileptogenic process in malnourished individuals. Conclusion: Malnutrition negatively changes the epileptogenic circuitry.

Keywords: Malnutrition, programming, epilepsy, experimental models of epilepsy, Status Epilepticus.

RESUMO

Desnutrição e epilepsia experimental


Unitermos: desnutrição, programação, epilepsia, modelos experimentais de epilepsia, status epilepticus.
INTRODUCTION

Environmental influences early in an organism's life can have long-term consequences.\textsuperscript{1,2} For example, nutritional restriction during the perinatal period can permanently affect morphofunctional patterns in a variety of physiological systems, including the nervous system. In rats, experimental models of maternal nutritional restriction are used for investigating the short- and long-term consequences of nutritional restriction on the nestling's growth.\textsuperscript{3} These effects involve a mechanism called "programming", in which an environmental stress during a critical developmental period has permanent effects on the structure and function of the organs.\textsuperscript{1,2}

An adequate nutritional state is essential to normal functioning, development, and aging of the central nervous system (CNS).\textsuperscript{4} When it comes to brain development should be considered not only in the growth of the organ, but especially in the synthesis of important cellular components such as nucleic acids and proteins in parallel with neurogenesis and gliogenesis, migration of neurons and glial cells, and differentiation cellular.\textsuperscript{5} It is known that malnutrition adversely affects nervous system maturation and functional development.\textsuperscript{6-7} Given this scenario, maternal malnutrition may interfere in some of these developmental stages of the fetal brain.\textsuperscript{4} In rodents, the malnutrition causes changes in neurotransmitter release and neuroplasticity and decreases the size of the brain.\textsuperscript{4,5} It’s known that malnutrition is a serious disease and that is related to a worse prognosis in the case of various neurological diseases such as epilepsy. Malnutrition is not a direct cause of epilepsy,\textsuperscript{8} but in previous studies it is has been reported that it might reduce the seizure threshold.\textsuperscript{8-9} Several reports using animal models have suggested that epilepsy and malnutrition are related.\textsuperscript{8} Hemb and collaborators\textsuperscript{10} showed that malnutrition and seizures have an additive detrimental effect on body and brain weight as well as on spatial learning and memory processing.

Epilepsies are characterized by spontaneous recurrent seizures, caused by focal or generalized paroxysmal changes in neurological functions triggered by abnormal electrical activity in the cortex\textsuperscript{11}. It is one of the most prevalent neurological conditions and it’s independent of age, racial, social class, geographic, or national boundaries.\textsuperscript{12} The most common risk factors for epilepsy are cerebrovascular disease, brain tumors, alcohol, traumatic head injuries, malformations of cortical development, genetic inheritance, and infections of the central nervous system.\textsuperscript{13} In resource-poor countries, endemic infections, such as malaria and neurocysticercosis, seem to be major risk factors.\textsuperscript{13} Approximately 50 million people throughout the world suffers from epilepsy, making it the second most common neurologic disorder (after stroke), affecting more than 2 million persons in the United States.\textsuperscript{14-15} Acquired, localization-related epilepsies, are the most common epilepsy syndromes with temporal lobe epilepsy comprising the majority.\textsuperscript{16} Not only is temporal lobe epilepsy (TLE) the most common epilepsy in adults, it is often refractory to medical therapy. Epidemiological studies suggest that between 70 and 80% of people developing epilepsy will go into remission, while the remaining patients continue to have seizures and are refractory to treatment with the currently available therapies.\textsuperscript{17-18} A prominent feature of temporal lobe epilepsy, and all acquired epilepsies, is a latency of months to years between the initial insult and the development of spontaneous seizures, the so-called silent period.\textsuperscript{19} Although some recent work suggests that epileptiform activity is not truly silent during this interval, it is during this period of relative quiescence that deleterious changes in cellular organization/connectivity and molecular expression develop to the point of overt spontaneous seizure generation.\textsuperscript{19} Experimental and clinical evidence suggests that "seizures beget seizures", implying a continued pattern of injury and reinforcement of the maladaptive processes producing the epileptic condition.\textsuperscript{20}

Much of what is known regarding the cellular and molecular basis of epileptogenesis has been learned from animal models\textsuperscript{21}. Thus, the objective of this review is to relate the model programming by malnutrition and its implications on experimental epilepsy.

MALNUTRITION

Morphological and functional characteristics in mammals develop according to the individual genome.\textsuperscript{22} However, there is a growing body of evidence from epidemiological studies in humans and from controlled investigations in animal models that genome regulation is largely modified by the nutritional environment such as an amount and composition of nutrients available to the offspring during prenatal and neonatal periods.\textsuperscript{23-27} There are numerous studies showing that a suboptimal intrauterine environment, as well as suboptimal nutrition during early neonatal life alters development.\textsuperscript{22} This situation can predispose the individual to lifelong health problems like metabolic syndrome or related diseases (such as glucose intolerance, insulin resistance, cardiovascular disease, hypertension, and obesity).\textsuperscript{23-24,27-31} These observations are in keeping with the predictive adaptive response hypothesis,\textsuperscript{31} an extension of Hales and Barker’s thrifty phenotype hypothesis\textsuperscript{32} or the fetal origins hypothesis.\textsuperscript{33} This phenomenon has been termed nutritional, developmental or metabolic programming which frequently involves intrauterine growth retardation (IUGR) or nutritional inadequacies during early postnatal life.\textsuperscript{22} Thus, programming is defined as the induction,
silencing or restriction of development of a permanent somatic structure or physiological system with long term effects for function.\textsuperscript{35} This may be caused by stimuli or disturbing factors (e.g. nutritional insults) acting during a sensitive time period (i.e. time of maximal growth of a tissue) or being a line of consecutive events affecting fetal growth quality.\textsuperscript{36-35} Programming is based on the observation that environmental changes can reset the developmental path during a critical period of life, when the tissues still have some plasticity and are in a higher proliferating and differentiating phase.\textsuperscript{36}

The programming hypothesis is supported by numerous examples of nutritional programming in experimental animals.\textsuperscript{37} In rats, maternal protein restriction in pregnancy leads to higher blood pressure,\textsuperscript{39} impaired glucose tolerance,\textsuperscript{39} insulin resistance,\textsuperscript{40-41} and altered hepatic architecture and function\textsuperscript{42} in the adult offspring. Moreover, malnutrition produces adverse functional effects such as loss of muscle mass and alteration of the immune system increasing the risk of infections that have clinical and public-health consequences.\textsuperscript{43} Toscano e colls.\textsuperscript{46} reported that low-protein intake during a critical period of development induces changes in the structure and function of skeletal muscle, compromising an animal's posture and locomotion. On another point of view, research has indicated that the protein restriction during gestation and lactation induces long-lasting alterations in the microstructure of feeding characterised by a delayed appearance of satiety and increased meal size.\textsuperscript{44} Corroborating this information, Souza and colls.\textsuperscript{45} has shown that protein restriction during perinatal development attenuates the inhibitory action of serotonin (5-HT) on food intake via a reduced sensitivity of 5-HT1B receptors, explaining that the hyperphagia associated with metabolic programming is at least partially related to a reduced regulatory function of 5-HT on food intake. Still trying of dietary imbalances, Borba and colls.\textsuperscript{47} in a two-generation study related for the first time, an impairing effect of long-lasting essential fat acids (EFA) deficiency on cortical spreading depression propagation in the rat cortex, which persisted in the second generation EFA-deficient animals. This suggests that factors in the prenatal and early postnatal environments can program an individual for an increased risk of certain diseases in later life.\textsuperscript{48}

Frías and colls.\textsuperscript{49} concluded that early malnutrition produces an alteration of the electrical cerebral activity pattern characterized by the prevalence of slow waves: delta and theta rhythms. These waves present lower frequency and greater amplitude which is characteristic in an immature brain and consisted in a delay in brain development.\textsuperscript{49} Findings from several studies have indicated that malnutrition during the fetal and neonatal stages can lead to potentially irreversible neuropahtological consequences. In animal models, it is well-known that early malnutrition has repercussions on exploratory behavior\textsuperscript{50} and memory.\textsuperscript{55} In humans, restricted nutrition increases the risk of psychiatric and psychosocial disorders, such as depression,\textsuperscript{52} schizophrenia,\textsuperscript{53} and aggressive behavior.\textsuperscript{54} as well neurological disorders as the epilepsy.\textsuperscript{55}

Links between malnutrition and epilepsy are complex. The malnutrition, via different mechanisms, could favour seizure onset and perhaps epilepsy. A better understanding of the interactions between malnutrition and epilepsy might be possible using an experimental model of malnutrition subjected to experimental epilepsy. Furthermore, it is important to know how the perinatally malnourished animals behave in the face of this extremely aggressive neurological disease.

**EXPERIMENTAL EPILEPSY**

Currently a lot of information about the cellular and molecular basis of epileptogenesis were obtained from animal models.\textsuperscript{21} Epileptogenesis refers to the events by which the normal brain becomes capable of producing epileptic seizures, i.e., the process by which neural circuits are converted from normal excitability to hyperexcitability.\textsuperscript{56}

As enumerated by White,\textsuperscript{21} an appropriate animal model of epileptogenesis should share characteristics with human epilepsy, including similar pathology, a latent period following initial insult, chronic hyperexcitability and spontaneous seizures. Manipulations that produce prolonged seizures (Status Epilepticus – SE) in experimental animals have proven to satisfy all these criteria.\textsuperscript{37} Among the models where one can observe the occurrence of SE are intraperitoneal or intra-hippocampal pilocarpine or kainic acid,\textsuperscript{19,58-60} electrical stimulation of the ventral hippocampus ventral,\textsuperscript{61-62} stimulation via perforating,\textsuperscript{63} and, finally electrical stimulation of the amygdale.\textsuperscript{64} Kindling is another model of epileptogenesis, does not produce SE, that consist of repeated stimulation, electrical or chemical, of various structures of the limbic system (usually amygdala, cortex and hippocampus), so that over time there is an increased excitability and the neurons become “pathological neurons” capable of generating epileptic crises, first, when they are stimulated and, subsequently, in some animal models, also spontaneously.\textsuperscript{65} Additional models of acquired epilepsy are based on the introduction of a focal cortical lesion and include the freeze-lesion, alumina gel lesion models, and cerebral hypoxia/ischemia.\textsuperscript{57} In vitro models of epileptiform activity involve exogenous treatments that increase neuronal excitability.\textsuperscript{57}

Although these in vitro treatments do not strictly relate to the acquired epilpsies, they highlight mechanisms contributing to hyperexcitability and include GABA<sub>A</sub> receptor blockade (bicuculline, penicillin), potassium...
channel inhibition with 4-aminopyridine (4-AP), elevated extracellular potassium, and zero magnesium-containing solutions\(^\text{60}\) (Table 1).

Table 1. Experimental models of acquired epilepsy.

<table>
<thead>
<tr>
<th>Status epilepticus</th>
<th>Kainic acid</th>
<th>Pilocarpine</th>
<th>Electrical stimulation</th>
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<tbody>
<tr>
<td>Traumatic injury</td>
<td>Fluid percussion injury</td>
<td>Cortical undercut</td>
<td>Alumina gel lesion</td>
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<td></td>
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<td>Alumina gel lesion</td>
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<td>Kindling model</td>
<td>Repeated, subthreshold electrical Stimulation</td>
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<td>Febrile seizures</td>
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Adjusted of Ransom & Blumenfeld.\(^\text{57}\)

The model of pilocarpine (PILO) has been widely used due to the technical facility and primarily by the pathophysiological similarity to human temporal lobe epilepsy.\(^\text{66}\) The systemic administration of the potent muscarinic agonist pilocarpine in rats promotes sequential behavioral and electrographic changes that can be divided into 3 distinct periods: (a) an acute period that built up progressively into a limbic Status Epilepticus and that lasts 24 h, (b) a silent period with a progressive normalization of EEG and behavior which varies from 4 to 44 days, and (c) a chronic period with spontaneous recurrent seizures (SRSs). The main features of the SRSs observed during the long-term period resemble those of human complex partial seizures and recur 2-3 times per week per animal.\(^\text{19}\) The induction of status epilepticus by pilocarpine leads to severe and widespread cell loss in several brain areas.\(^\text{86}\) The initial damage, occurring a few hours after the onset of Status Epilepticus, is most intense in the superficial layers of some neocortical areas, hilus of the hippocampus, endopiriform nucleus, piriform cortex and claustrum. Eight hours after SE onset, damage has further intensified in those areas and, in addition, becomes significant in entorhinal cortex, amygdaloïd nuclei, ventromedial nucleus of the hypothalamus, subiculum and the bed nucleus of the stria terminalis. Damage in these distinct brain areas is time-specific.\(^\text{19,60}\) Evidence of altered cell morphology in the pilocarpine model has been provided mostly for the hippocampus.\(^\text{67}\) Altered distribution of dendritic spines in dentate granule cells and distorted dendritic trees in putative GABAergic hippocampal interneurons are some of these changes.\(^\text{19,66}\) Additional morphological changes are the emergence of axonal sprouting – the most notable being the supragranular mossy fiber sprouting, granule cell dispersion, increased rate of neurogenesis, and development of granule cell basal dendrites.\(^\text{19,60}\) Different works have demonstrated that long-lasting seizures unchain a complex chemical cascade, triggering neurochemical alteration in neurons and glial cells.\(^\text{66}\) These immediate or long-lasting events can modify the cellular environment through changes of ionic gradient across the cell membrane, alteration of gene expression such as receptors, trophic factors, enzymes, proteins from cytoskeleton, protein from matrix and the phosphorylation of macromolecules.\(^\text{66}\) Furthermore, seizures can induce reactive gliosis generated by cell death and induced by these long-lasting convulsions.\(^\text{67}\) These modifications promote synaptic remodeling, which can change the excitability of neurons from temporal structures, leading to the appearance of brain damage and a permanent hyperexcitability.\(^\text{56}\)

The silent phase of pilocarpine model is marked by an important unbalance between inhibition and excitation.\(^\text{68}\) The decreased concentration of GABA in the hippocampus, during the silent period, could suggest an increased consumption of this amino acid in attempt to control the tissue excitability. In contrast, the increased concentration of glutamate in the hippocampus could suggest a potential excitatory pathway of this structure, probably responsive for the appearance of spontaneous seizures.\(^\text{66}\) Thus, according to several authors, the temporal lobe epilepsy has been related to excessive excitability in limbic structures, low function of inhibitory pathways or the association between both events.\(^\text{69}\) As a consequence of neurotransmission alteration, the transduction signal through plasma membrane is also modified, changing neuronal metabolism and genes expression.\(^\text{19}\)

Experimental models in animals may represent a useful tool, both in elucidating the pathophysiological mechanisms of epilepsy and in identifying treatments, not only with antiepileptic effect, but also antiepileptogenic. Further research in the question is needed, as well as the use of valid experimental models. This is not only due to the high prevalence/incidence of this disease, but also because of the lack of effective treatments and the devastating consequences that it can have on the patients and their families.

**MALNUTRITION AND EPILEPSY**

Epilepsy and malnutrition represent two important health problems because of their serious medical, social, cultural, and economic implications.\(^\text{70-71}\) It is known that a malnutrition contributes to the high prevalence of epilepsy especially in developing countries.\(^\text{72-73}\) There are several hypotheses about the possible mechanisms involved like the reduction of the seizure threshold or an immunological vulnerability.\(^\text{74}\) Biochemical alterations due to malnutrition...
like electrolyte abnormalities and hypoglucemia could affect seizure threshold\textsuperscript{15–16}. Studies show that malnutrition reduces resistance to infection\textsuperscript{17}, this can make malnourished people or animals more vulnerable to a range of infections including neurotropic infections that cause epilepsy and which are prevalent in developing countries\textsuperscript{18}. Palencia and colls.\textsuperscript{3} used a rat model of chronic malnutrition to study the possible influence of malnutrition at late stages of brain development with experimental seizures induced by pentylenetetrazole (PTZ), a GABA\textsubscript{A} receptor antagonist. In this study, the threshold and dose of PTZ required to produce seizures were reduced in malnourished rats.

The relationship between malnutrition and epilepsy is ancient, but little has been investigated about her. The experimental models are useful to broaden the knowledge about what the real implications of epilepsy in malnourished.

**CONCLUSIONS**

Studies emphasize the association between malnutrition and epilepsy. Animals programmed by malnutrition are an interesting alternative to investigate how the epileptogenic mechanisms are developed in these animals. It is clear that malnutrition negatively alters the epileptogenic circuits in epileptic because changes the plasticityd cerebral, but papers relating malnutrition and epilepsy are rare in the literature.

**REFERENCES**

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