Malnutrition and experimental epilepsy

Tâmara Kelly de Castro Gomes[a], Suzana Lima de Oliveira[a], Raul Manhães de Castro[b]

Faculdade de Nutrição – Universidade Federal de Alagoas

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

Introdução: Perturbações ao ambiente intrauterino podem ter efeitos prejudiciais sobre o feto e consequências patológicas persistentes ao longo da adolescência e da idade adulta. Restrição protéica durante o período pré-natal tem repercussões significativas sobre a ontogenia e o desenvolvimento do sistema nervoso central. Restrição alimentar nessa fase da vida aumenta o risco de distúrbios neurológicos como a epilepsia. **Objetivo**: Relacionar o modelo de programação pela desnutrição e suas implicações na epilepsia experimental. **Material e Métodos**: Procedeu-se a pesquisa em artigos científicos publicados nos Bancos de Dados Medline, PubMed, Periódicos CAPES, ScienceDirect e Scielo. As palavras-chave selecionadas para a pesquisa incluíram epilepsia, *status epilepticus*, pilocarpina, desnutrição, programming. **Resultados e Discussão**: Diversos estudos realizados em modelos animais ou humanos destacam os possíveis efeitos adversos da desnutrição no início das crises epilépticas. A vulnerabilidade imunológica, alterações bioquímicas como anormalidades eletrolíticas e hipoglicemia podem ser os fatores responsáveis pela intensificação dos processos epileptogênicos em indivíduos desnutridos. **Conclusão**: A desnutrição altera negativamente a circuitaria epileptogênica.

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

INTRODUCTION

Environmental influences early in an organism's life can have long-term consequences.[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.[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.[1-2]

An adequate nutritional state is essential to normal functioning, development, and aging of the central nervous system (CNS).[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.[5] It is known that malnutrition adversely affects nervous system maturation and functional development.[6-7] Given this scenario, maternal malnutrition may interfere in some of these developmental stages of the fetal brain.[4] In rodents, the malnutrition causes changes in neurotransmitter release and neuroplasticity and decreases the size of the brain.[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,[8] but in previous studies it is has been reported that it might reduce the seizure threshold.[8-9] Several reports using animal models have suggested that epilepsy and malnutrition are related.[8] Hemb and collaborators[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[11]. It is one of the most prevalent neurological conditions and it's independent of age, racial, social class, geographic, or national boundaries.[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.[13] In resource-poor countries, endemic infections, such as malaria and neurocysticercosis, seem to be major risk factors.[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.[14-15] Acquired, localization-related epilepsies, are the most common epilepsy syndromes with temporal lobe epilepsy comprising the majority.[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.[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.[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.[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.[20]

Much of what is known regarding the cellular and molecular basis of epileptogenesis has been learned from animal models[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.[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.[23-27] There are numerous studies showing that a suboptimal intrauterine environment, as well as suboptimal nutrition during early neonatal life alters development.[22] This situation can predispose the individual to lifelong health problems like metabolic syndrome or related diseases (such as glucose intolerance, insulin resistance, cardio-vascular disease, hypertension, and obesity).[23-24,27-31] These observations are in keeping with the predictive adaptive response hypothesis,[31] an extension of Hales and Barker's thrifty phenotype hypothesis[32] or the fetal origins hypothesis.[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.[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.[22] 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.[34-35] 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.[36]

The programming hypothesis is supported by numerous examples of nutritional programming in experimental animals.[37] In rats, maternal protein restriction in pregnancy leads to higher blood pressure,[38] impaired glucose tolerance,[39] insulin resistance,[40-41] and altered hepatic architecture and function[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.[43] Toscano e colls.[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.[44] Corroborating this information, Souza and colls.[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.[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.[48]

Frías and colls.[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.[49] Findings from several studies have indicated that malnutrition during the fetal and neonatal stages can lead to potentially irreversible neuropathological consequences. In animal models, it is well-known that early malnutrition has repercussions on exploratory behavior[50] and memory.[51] In humans, restricted nutrition increases the risk of psychiatric and psychosocial disorders, such as depression,[52] schizophrenia,[53] and aggressive behavior,[54] as well neurological disorders as the epilepsy.[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.[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.[56] As enumerated by White,[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[57]. Among the models where one can observe the occurrence of SE are intraperitoneal or intra-hippocampal pilocarpine or kainic acid,[19,58-60] electrical stimulation of the ventral hippocampus ventral,[61-62] stimulation via perforating,[63] and, finally electrical stimulation of the amygdale.[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.[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.[57] *In vitro* models of epileptiform activity involve exogenous treatments that increase neuronal excitability.[57] Although these *in vitro* treatments do not strictly relate to the acquired epilepsies, they highlight mechanisms contributing to hyperexcitability and include $GABA_A$ receptor blockade (bicuculline, penicillin), potassium

channel inhibition with 4-aminopyridine (4-AP), elevated extracellular potassium, and zero magnesium-containing solutions[57] (Table 1).

Table 1. Experimental models of acquired epilepsy.

Status epilepticus	Kainic acid
	Pilocarpine
	Electrical stimulation
Traumatic injury	Fluid percussion injury
	Cortical undercut
	Alumina gel lesion
	Freeze lesion
	Ferric chloride injection
Kindling model	Repeated, subthreshold electrical
	Stimulation
Febrile seizures	Hyperthermia

Adjusted of Ransom & Blumenfeld.[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.[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 recurs 2-3 times per week per animal.[19] The induction of status epilepticus by pilocarpine leads to severe and widespread cell loss in several brain areas.[66] 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, amygdaloid nuclei, ventromedial nucleus of the hypothalamus, subiculum and the bed nucleus of the stria terminalis. Damage in these distinct brain areas is time-specific.[19,60] Evidence of altered cell morphology in the pilocarpine model has been provided mostly for the hippocampus.[67] Altered distribution of dendritic spines in dentate granule cells and distorted dendritic trees in putative GABAergic hippocampal interneurons are some of these changes.[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.[19,60] Different works have demonstrated that long-lasting seizures unchain a complex chemical cascade, triggering neurochemical alteration in neurons and glial cells.[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.[66] Furthermore, seizures can induce reactive gliosis generated by cell death and induced by these long-lasting convulsions.[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.[66]

The silent phase of pilocarpine model is marked by an important unbalance between inhibition and excitation[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[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[69]. As a consequence of neurotransmission alteration, the transduction signal through plasma membrane is also modified, changing neuronal metabolism and genes expression[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[70-71]. It is known that a malnutrition contributes to the high prevalence of epilepsy especially in developing countries[72-73]. There are several hypotheses about the possible mechanisms involved like the reduction of the seizure threshold or an immunological vulnerability[74]. Biochemical alterations due to malnutrition

like electrolyte abnormalities and hypoglycemia could affect seizure threshold[75-76]. Studies show that malnutrition reduces resistance to infection[77], 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[78]. Palencia and colls.[8] 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 pentylentetrazole (PTZ), a $GABA_A$ 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 plasticydad cerebral, but papers relating malnutrition and epilepsy are rare in the literature.

REFERENCES

1. Barker DJ. The origins of the developmental origins theory. J Intern Med 2007;261(Suppl 5):412-7.

2. Lucas A. Long-term programming effects of early nutrition – implications for the preterm infant. J Perinatol 2005;25(Suppl 2):2S-6S.

3. Desai M, Crowther NJ, Lucas A, Hales CN. Organ-selective growth in the offspring of protein-restricted mothers. Br J Nutr 1996;76(Suppl 4):591-603.

4. Rotta LN, Schmidt AP, Souza TM, Nogueira CW, Souza KB, Izquierdo IA, Perry MLS, Souza DO. Effects of undernutrition on glutamatergic parameters in rat brain. Neurochem Res 2003;28(Suppl 8):1181-86.

5. Morganne PJ, Monkler DJ, Galler JR. Effects of prenal protein malnutrition on the hippocampal formation. Neurosci Biobehav Rev 2002;26(Suppl 4):471-83.

6. Morgane PJ, Austin-lafrance RJ, Bronzino J, Tonkiss J, Diaz-Cintra S, Cintra L, Kemper T, Galler JR. Prenatal malnutrition and development of the brain. Neurosci Biobehav Rev 1993;17:91-128.

7. Duran P, Galván A, Granados L, Aguilar-Roblero R, Cintra L. Effects of protein malnutrition on vigilance state and their circadian rhythms in 30- day old rats submitted total sleep deprivation. Nutr Neurosci 1999;2: 127-38.

8. Palencia G, Calvillo M, Sotelo J. Chronic malnutrition caused by a corn-based diet lowers the threshold for pentylenetetrazol-induced seizures in rats. Epilepsia 1996;37:583-6.

9. Stern WC, Forbes WB, Resnick O, Morgane PJ. Seizure susceptibility and brain amine levels following protein malnutrition during development in the rat. Brain Res 1974;79:375-84.

10. Hemb M, Cammarota M, Nunes ML. Effects of early malnutrition, isolation and seizures on memory and spatial learning in the developing rat. Int J Devl Neuroscience 2010;28:303-7.

11. Dichter MA. Emerging insights into mechanisms of epilepsy: implications for new antiepileptic drug development. Epilepsia 1994;35(Suppl 4):S51-S57.

12. de Boer HM, Mula M, Sander JW. The global burden and stigma of epilepsy. Epilepsy Behav 2008;12:540-6.

13. Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. Lancet 2006;367:1087-100.

14. Theodore WH, Spencer SS, Wiebe S, Langfitt J T, Ali A, Shafer PO, Berg AT, Vickrey BG. Epilepsy in North America: A report prepared under the auspices of the Global Campaign against Epilepsy, the International Bureau for Epilepsy, the International League Against Epilepsy, and the World Health Organization. Epilepsia 2006;47: 1700-22.

15. Epilepsy: aetiogy, epidemiology and prognosis. Fact sheet. Word Health Organisation; 2001.

16. Zarrelli, MM, Beghi E, Rocca WA, Hauser WA. Incidence of epileptic syndromes in Rochester, Minnesota: 1980-1984. Epilepsia 1999;40,1708-14.

17. Kwan P, Sander JW. The natural history of epilepsy: an epidemiological view. J Neurol Neurosurg Psychiatry 2004;75:1376-81.

18. Sander JW. The epidemiology of epilepsy revisited. Curr Opin Neurol 2003;16:165-70.

19. Cavalheiro EA. 1995. The pilocarpine model of epilepsy. Ital J Neurol Sci 16:33-7.

20. Berg AT, Shinnar S. Do seizures beget seizures? An assessment of the clinical evidence in humans. J Clin Neurophysiol 1997;14:102-10.

21. White HS. Animal models of epileptogenesis. Neurology 2002;59: 7-14.

22. Guilloteau P, Zabielski R, Hammon HM, Metges CC. Adverse effects of nutritional programming during prenatal and early postnatal life, some aspects of regulation and potential prevention and treatments. J Physiol Pharmacol. 2009;60 Supp 3:17-35.

23. Godfrey KM, Barker DJ. Fetal programming and adult health. Publ Health Nutr 2001;4(Suppl 2B):611-24.

24. Gluckman PD, Hanson MA, Spencer HG, Bateson P. Environmental influences during development and their later consequences for health and disease: implications for the interpretation of empirical studies. Proc Biol Sci 2005;272:671-7.

25. Budge H, Gnanalingham MG, Gardner DS et al. Maternal nutritional programming of fetal adipose tissue development: long-term consequences for later obesity. Birth Defects Res C Embryo Today 2005;75:193-9.

26. Wu G, Bazer FW, Wallace JM, Spencer TE. Board-invited review – intrauterine growth retardation: implications for the animal sciences. J Anim Sci 2006;84:2316-37.

27. Symonds ME, Stephenson T, Gardner DS, Budge H. Longterm effects of nutritional programming of the embryo and fetus: mechanisms and critical windows. Reprod Fertil Dev 2007;19:53-63.

28. Langley-Evans SC. Developmental programming of health and disease. Proc Nutr Soc 2006;65(Suppl 1):97-105.

29. Nathanielsz PW. Animal models that elucidate basic principles of the development origins of adult diseases. ILAR Journal 2006;47: 73-82.

30. Procter KL. The aetiology of childhood obesity: a review. Nutr Res Rev 2007;20:29-45.

31. Khan IY, Dekou V, Hanson MA, Poston L, Taylor PD. Predictive adaptative response to maternal high-fat diet, prevent endothelial dysfunction but not hypertension in adult rat offspring. Circulation 2004;110:1097-102.

32. Hales CN, Barker DJ. The thrifty phenotype hypothesis. Br Med Bull 2001;60:5-20.

33. Barker DJP. Fetal origins of coronary heart diseases. Brit Med J 1995; 311:171-4.

34. Harding JE. The nutritional basis of the fetal origins of adult disease. Int J Epidemiol 2001;30:15-23.

35. Mc Millen JC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. Physiol Rev 2005;85:571-633.

36. de Moura EG, Lisboa PC, Passos MC. Neonatal programming of neuroimmunomodulation- role of adipocytokines and neuropeptides. Neuroimmunomodulation 2008;15:176-88.

37. Fall C. Maternal nutrition: Effects on health in the next generation. Indian J Med Res 2009;130:593-9.

38. Langley SC, Jackson AA. Increased systolic blood pressure in adult rats induced by fetal exposure to maternal low protein diets. Clin Sci 1994;86:217-22.

39. Ozanne SE, Hales CN. The long-term consequences of intrauterine protein malnutrition for glucose metabolism. Proc Nutr Soc 1999;58:615-9.

40. Ozanne SE, Dorling MW, Wang CL, Nave BT. Impaired PI 3-kinase activation in adipocytes from early growth-restricted rats. Am J Physiol 2001;280:534-9.

41. Vickers MH, Breier BH, Cutfield WS, Hofman PL, Gluckman PD. Fetal origins of hyperphagia, obesity, and hypertension and postnatal amplification by hypercaloric nutrition. Am J Physiol Endocrinol Metab 2000;279:83-7.

42. Hales CN, Desai M, Ozanne SE, Crowther NJ. Fishing in the stream of diabetes: from measuring insulin to the control of fetal organogenesis. Biochem Soc Trans 1996; 24:341-50.

43. Stratton RJ, Green CJ, Elia M. Disease-related malnutrition: an evidence-based approach to treatment. CABI Pub,Wallingford, UK; Cambridge, MA; 2003.

44. Orozco-Solis R, Souza SL, Matos RJB, Grit, I, Le Bloch J, Nguyen P, Manhães-de-Castro R, Bolaños-Jiménez F. Perinatal undernutrition-induced obesity is independent of the developmental programming of feeding. Physiology & Behavior 2009;96:481-92.

45. Souza SL, Orozco-Solis R, Grit, I, Manhães-de-Castro R, Bolaños-Jiménez F. Perinatal protein restriction reduces the inhibitory action of serotonin on food intake. Eur J Neurosci 2008;27:1400-8.

46. Toscano AE, Manhães-de-Castro R, Canon F.Effect of a low-protein diet during pregnancy on skeletal muscle mechanical properties of offspring rats. Nutrition 2008;24(Suppl 3):270-8.

47. Borba JMC, Rocha-de-Melo AP, Santos AA, Costa BLSA, Silva RP, Passos PP, Guedes RCA. Essential fatty acid deficiency reduces cortical spreading depression propagation in rats: a two-generation study. Nutr Neurosci 2010;13(Suppl 3):144-50.

48. Chen J, Xu H, Shen Q, Guo W, Sun L. Effect of postnatal high-protein diet on kidney function of rats exposed to intrauterine protein restriction. Pediatr Res 2010;68(Suppl 2):100-4.

49. de Frías V, Varela O, Oropeza JJ, Bisiacchi B, Álvarez A. Effects of prenatal protein malnutrition on the electrical cerebral activity during development. Neurosci Lett 2010;482:203-7.

50. Almeida SS, Tonkiss J, Galler JR. Prenatal protein malnutrition affects exploratory behavior of female rats in the elevated plus-maze test. Physiol. Behav 1996;60:675-80.

51. Tonkiss J, Schultz PL, Shumsky JS, Fiacco TTA, Vincitore M, Rosene DL, Galler JR. Chlordiazepoxide-induced spatial learning deficits: dose-dependent differences following prenatal malnutrition. Pharmacol. Biochem. Behav 2000;65:105-16.

52. Susser E, Hoek HW, Brown A. Neurodevelopmental disorders after prenatal famine: the story of the Dutch famine study. Am J Epidemiol 1998;147:213-6.

53. St Clair D, Xu M, Wang P, Yu Y, Fang Y, Zhang F, Zheng X, Gu N, Feng G, Sham P, He L. Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959-1961. JAMA 2005;294:557-62.

54. Liu J, Raine A. The effect of childhood malnutrition on externalizing behaviour. Curr Opin Pediat 2006;18:565-70.

55. Crepin S, Godet B, Chassain B, Preux PM, Desport JC. Malnutrition and epilepsy: A two-way relationship. Clinical Nutrition 2009;28:219-25.

56. Santos NF, Arida RM, Trindade Filho EM, Priel MR, Cavalheiro EA. Epileptogenesis in immature rats following recurrent status epilepticus. Brain Res Rev 2000;32:269-76.

57. Ransom CB, Blumenfeld H. Acquired Epilepsy: Cellular and Molecular Mechanisms. In: Waxman SG. Molecular Neurology. London: Elsevier; 2007. p. 360-70.

58. Cavalheiro, EA, Leite JP, Bortolotto A, Turski WA, Ikonomidou C, Turski L. Long-term effects of pilocarpine in rats: structural damage of the brain triggers kindling and spontaneous recurrent seizures. Epilepsia 1991;32(Suppl 6):778-82.

59. Furtado MA, Braga GK, Oliveira JAC, Del Vecchio F, Garcia-Cairasco N. Behavioral, Morphologic, and Electroencephalographic Evaluation of Seizures Induced by Intrahippocampal Microinjection of Pilocarpine. Epilepsia 2002;43(Suppl 5):37-9.

60. Leite JP, Bortolotto ZA, Cavalheiro EA. Spontaneous recurrent seizures in rats: An experimental model of partial epilepsy. Neurosc Biobehav Rev 1990;14:511-7.

61. Lothman EW, Bertram EH, Bekenstein JW, Perlin JB. Self-sustaing limbic status epilepticus induced by "continuous" hipocampal stimulation: electrographic and behavioral characteristics. Epilepsy Res 1989;3:107-19.

62. Bertram EH, Cornett JF. The evolution of a rat model of chronic limbic seizures. Brain Res 1994;661:157-62.

63. Shirasaka Y, Wasterlain CG. Chronic epileptogenicity following focal status epilepticus. Brain Res 1994;655:33-44.

64. Nissinen J, Halonen T, Koivisto E, Pitkanen A. A new model of chronic temporal lobe epilepsy induced by electrical stimulation of the amygdala in rat. Epilepsy Res 2000;38:177-205.

65. Garcia MEG, Morales IG, Guiu JM. Experimental models in epilepsy. Neurología 2010;25(Suppl 3):181-88.

66. Scorza FA, Arida RM, Naffah-Mazzacoratti MG, Scerni DA, Cavalheiro EA. The pilocarpine model of epilepsy: what have we learned? An Acad Bras Cienc 2009;81(Suppl 3):345-65.

67. Andrade-Valença LPA, Valença MM, Velasco TR, Leite JP. Epilepsia do lobo temporal mesial associada à esclerose hipocampal. J Epilepsy Clin Neurophysiol 2006;12(Suppl 1):31-6.

68. Cavalheiro EA, Fernandes MJ, Turski L, Naffah-Mazzacoratti MG. Spontaneous recurrent seizures in rats: amino acid and monoamine determination in the hippocampus. Epilepsia 1994;35(Suppl 1):1-11.

69. Meldrum BS. Neurochemical sustrates of ictal behavior. Adv Neurol 1991;55:35-45.

70. Meinardi H, Scott RA, Reis R, Sander JW. ILAE Commission on Developing World. The treatment gap in epilepsy: the current situation and ways forward. Epilepsia 2001; 42:136-49.

71. Food and Agriculture Organisation. (2006) available at http://www.fao.org/ag/agn/nutrition/ben-e.stm (accessed February 22, 2006).

72. Hackett R, Iype T. Malnutrition and childhood epilepsy in developing countries. Seizure 2001;10:554-8.

73. Crepin S, Houinato D, Nawana B, Avode GD, Preux PM, Desport JC. Link between Epilepsy and Malnutrition in a Rural Area of Benin. Epilepsia 2007;48(Suppl 10):1926-33.

74. Andrade JP, Paula-Barbosa MM. Protein malnutrition alters the cholinergic and GABAergic systems to the hippocampal formation on the adult rat: an immunocytochemical study. Neurosci Lett 1996;211:211-5.

75. Bushinsky DA, Monk RD. Electrolyte quintet, Calcium. Lancet 1998; 352:306-11.

76. Kumar S, Berl T. Electrolyte quintet, Sodium. Lancet 1998;352:220-28.

77. Chandra RK. Nutrition and the immune system: an introduction. Am J Clin Nutr 1997;66:460-3.

78. Preux PM, Druet-Cabanac M. Epidemiology and aetiology of epilepsy in sub-Saharan Africa. Lancet Neurol 2005;4:21-31.

Endereço para correspondência:
Conjunto Medeiros Neto III – Bloco 25, ap. 303 – Tabuleiro dos Martins
57063-840, Maceió, AL, Brasil
E-mail: tkgomes@gmail.com