

NUTRITION AND NEURAL DEVELOPMENT: A CORTICAL SPREADING DEPRESSION (CSD) APPROACH

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Brain structural and functional maturation are programmed to occur in the rat primarily during the lactation period. An adequate nutrition beginning early in life is the basis for a good brain development and consequently also for brain function. Nutritional deficiency can alter neural development, and some of the neural effects of malnutrition are long-lasting; therefore, they can be observed in adulthood. Behavioral and electrophysiological alterations observed in early malnourished humans and in laboratory animals can be the consequence of malnutrition-induced changes in nerve cell structure and myelination pattern, as well as alterations in synaptic transmitters. Malnutrition-induced brain functional impairment also includes disturbances involving consciousness, emotion, learning, memory, and cognition. Observations of very low birthweight infants and children collectively indicate a causal relationship between impaired neurodevelopmental outcome and deficient behavioral processes involving reduced visual and verbal function, with negative consequences on the responses to novel and competitive situations.

In the malnourished rat, evidence points to increased susceptibility to neural excitability-related processes including experimentally induced seizures and the propagation of cortical spreading depression (CSD). CSD is a brain electrophysiological response first described in laboratory animals by Leão (J. Neurophysiol. 7:359, 1944) as a reversible and slowly propagated (propagation velocities in the order of a few mm/min) wave of reduction (depression) of the spontaneous and evoked electrical activity of the cerebral cortex in response to a mechanical, electrical and chemical stimulation of a point of the cortical tissue. More recently, CSD has been also documented in humans (Ann. Neurol. 63:720, 2008; Clin. Neurophysiol. 119:1973, 2008). Measuring CSD velocity of propagation along the cortical tissue is a reasonable and simple method for estimating brain CSD susceptibility under clinically relevant conditions known to influence brain excitability, like the nutritional and the pharmacological ones.

There is evidence that the critical time window for brain development is inhomogeneous with respect to distinct neural structures and developmental

processes. Evidence concerning brain electrical activity, implies that a deleterious factor like malnutrition would have the most important impact when acting at a certain point in time within the critical period. This evidence allows one to predict a similar heterogeneous pattern of brain developmental effects in the case of drugs like dipyrone. Experimental models devoted to studying the developmental consequences of pharmacological and nutritional factors on brain function may improve general understanding about the developmental processes of the nervous system, as well as its strategies for adaptation to external insults, which may be clinically relevant. When occurring early in life, such insults can modify the patterns of developmental processes in the brain, influencing brain functions as well as mechanisms of neural plasticity.

In this presentation, we would discuss some data from our laboratory demonstrating that, in the rat: 1) early malnutrition facilitates CSD propagation in adulthood; 2) when supplementing the diet with a low quality (vegetable) protein, the effects on CSD are not reverted; 3) reversion of CSD facilitation is achieved only when the protein used in the diet supplementation is of high quality (casein). Indeed, even short periods of malnutrition during lactation can long-lastingly facilitate SD propagation when the pups become adults. We also demonstrated that the CSD response of early-malnourished adult brains change when they are challenged by certain drugs of therapeutical use in humans, such as diazepam and glucose. The facilitating effect of RBD-malnutrition on CSD propagation has been causally associated, at least in part, with the brain changes induced by malnutrition, including: (1) disturbances in the action of synaptic neurotransmitters, (2) increase in the brain cell packing density, and (3) reduction in the myelination of the brain . An inverse correlation between brain myelination and CSD propagation has been recently demonstrated by employing dietary, genetic (transgenic animals), and immuno-histochemical approaches. These studies have also shown the dichotomous nature of the modulation of such an effect; CSD was accelerated in myelin-deficient and decelerated in hypermyelinated rodents. A similar diet-dependent dichotomous CSD modulation has also been demonstrated by comparing malnourished and over-nourished rats, with CSD acceleration in malnourished rats, and deceleration in over-nourished rats, as compared to the well-nourished controls. Also, drug-treatment (with dipyrone) for short periods within the critical phase of brain development has been shown to be able to modify brain CSD reaction shortly after weaning.

Data will be discussed on the basis of the importance of using the CSD phenomenon to study the nutritional and non-nutritional influences on brain development.

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