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RESEARCH ARTICLE

Potentiation of spontaneous and evoked cortical electrical activity after spreading depression: in vivo analysis in well-nourished and malnourished rats

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Abstract Cortical spreading depression (CSD) is influenced by brain excitability and is related to neurological diseases, such as epilepsy. In vitro evidence indicates that neuronal electrical activity is potentiated after CSD. Malnutrition can cause electrophysiological changes in the brain, both in animals and in humans. Here, we investigated in vivo whether CSD potentiates the amplitude of electrocorticogram (ECoG) and of transcallosal evoked responses in adult well-nourished (W), early-malnourished (M), and food-restricted rats. ECoG amplitudes were compared before and after CSD, at two parietal regions (designated the anterior and posterior regions). In the anterior region, post-CSD amplitudes of the ECoG waves were 13–23% higher ($P < 0.05$) than the pre-CSD values in all groups. In the posterior region, amplitudes increased 22% in the M group only ($P < 0.05$). In a fourth CSD-free group, ECoG amplitude did not change during the four recording hours. Transcallosal electrically evoked cortical responses also increased 21.5 ± 9.6% and 41.8 ± 28.5%, after CSD, in the W and M conditions, respectively, as compared to pre-CSD values. The data support the hypothesis of an in vivo CSD potentiation on cortical excitability as recorded by spontaneous and evoked electrical activity and modulation by nutritional status.

Keywords Brain excitability · Cerebral cortex · EEG · Rat · Transcallosal responses

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Introduction

Cortical spreading depression (CSD) has been experimentally described as a reversible and propagated wave of reduction in the spontaneous and evoked electrical activity of the cerebral cortex (Leão 1944). This phenomenon occurs in response to the electrical, chemical, or mechanical stimulation of one point on the cortical surface. Simultaneously with the EEG depression, a slow potential change (also called the DC potential change) of the tissue has been described (Leão 1947).

CSD intrinsic mechanisms and their possible association with brain disorders have not been fully characterized, but experimental evidence suggests strong connections between CSD- and excitability-related human neurological disorders like epilepsy, migraine, and brain ischemia (Leão 1944; Hadjikhani et al. 2001; Guedes 2005; Goadsby 2006; Moskowitz 2007; Berger et al. 2008). The appearance of abnormal, epileptiform EEG waves associated with CSD (Leão 1944; Guedes and Do Carmo 1980) led to the postulation of a CSD-related modulation in neural excitability and synaptic activity, with a possible implication for long-term potentiation (LTP; Footitt and Newberry 1998). LTP is characterized as an increase in postsynaptic responses that can last hours, days, or weeks after brief repetitive stimulation of pre-synaptic afferents. The phenomenon appears to occur as a consequence of a persistent increase in synaptic strength (neural plasticity), which has been

associated with learning and memory (e.g., Izquierdo et al. 2008). LTP has been largely investigated in the mammalian hippocampus in studies of synaptic plasticity and neuronal excitability. Despite much progress in efforts to elucidate the mechanisms of induction and expression of LTP, the factors responsible for the prolonged increase in synaptic efficacy during the phenomenon remain to be fully explained (Anwyl 2009). In addition, any possible relationship between CSD and LTP has yet to be investigated in vivo in the mammalian brain.

Previously, we investigated the effects of early nutritional deficiency on the speed of CSD propagation in adulthood (Rocha-de-Melo et al. 2006); however, no work has addressed possible changes induced by malnutrition in CSD-related cortical activity amplitude. Because alterations in anatomical, biochemical, and electrophysiological parameters of the brain can be caused by changes in the nutritional status of developing organisms (Barret and Radke-Yarrow 1985; Hack et al. 1991; Strupp and Levitsky 1995; Picanço-Diniz et al. 1998; Ranade et al. 2008), we aimed to investigate the effects of early malnutrition on cortical excitability as recorded by electrocorticography, as well as on transcallosal electrically driven evoked activities recorded by glass micropipettes in adult rats undergoing CSD. Animals previously were subjected to nutritional changes during the weaning period or to an acute period of 21 days of food restriction in adulthood. We hypothesized (1) a causal association between CSD and the potentiation of spontaneous and evoked cortical electrical activity and (2) that this potentiation is influenced by the early nutritional status of the adult animal but not by a short period of food restriction in adulthood (Morgane et al. 2002; Guedes 2005).

Methods

Animals and nutritional treatments

The 42 male Wistar rats used in this study were handled in accordance with the protocols of the Ethics Committee for Animal Research of the Universidade Federal de Pernambuco, which complies with the Principles of Laboratory Animal Care (National Institutes of Health, Bethesda, USA). They were kept in polypropylene cages (51 cm × 35.5 cm × 18.5 cm) in a room maintained at 22 ± 1°C with a 12:12 h light:dark cycle (lights on at 7:00 a.m.). Post-CSD potentiation was evaluated in 32 rats for spontaneous electrocorticogram (ECoG) activity and in 10 rats for the electrically driven transcallosal cortical evoked responses. The 32 animals in the ECoG study were distributed into three groups: well-nourished (W, $n = 15$), malnourished (M, $n = 10$), and food-restricted (FR, $n = 7$), according to nutritional status. Groups W and M were suckled in litters formed by 6 and 12 pups, respectively (Plagemann et al. 1999; Rocha-de-Melo et al. 2006). Increasing the number of pups per litter has proved to be effective in triggering a moderate degree of malnutrition during the lactation period (Rocha-de-Melo et al. 2006; Frazão et al. 2008). Group FR consisted of W rats subjected for 21 days (from postnatal days 70 to 90) to quantitative restriction of a laboratory chow diet. These animals received 70% of the amount of food consumed by age-matched well-nourished rats, as previously described (Wolff et al. 1999; Rich et al. 2010). All animals were suckled by dams fed a laboratory chow diet (Purina do Brazil Ltda), with 23% protein. The W and M groups were weighed on postnatal days 7, 14, 21, 30, 60, and 90. The FR group was weighed at 90 days.

Electrophysiological recordings

On the day of the electrophysiological recording, rats 90–120 days old were anesthetized by i.p. injection of a mixture of 1,000 mg/kg urethane plus 40 mg/kg chloralose (Sigma; 10 ml/kg). For the spontaneous activity recording (ECoG), three trephine holes were drilled on the right side of the skull. These holes were aligned in the frontal–occipital direction and parallel to the midline. The anterior hole (2 mm diameter), drilled at the frontal bone, was used to elicit CSD. The two other holes (2–3 mm diameter) in the parietal–occipital region served as recording places and were designated, respectively, as the *a* (anterior) and *p* (posterior) recording points. The ECoG and the DC potential of the cortical surface were continuously recorded for 4 h by means of two Ag–AgCl agar-Ringer electrodes (one in each hole), against a common reference electrode of the same type, placed on the nasal bone. During the two initial recording hours, no KCl stimulus was applied, and consequently no CSD was elicited (baseline period). In the last two recording hours, in 27 animals of the ECoG study (10 W, 10 M, and 7 FR rats), six CSD episodes were elicited at 20-min intervals by 1-min cortical stimulation with 2% KCl (CSD period). In each animal, we compared the amplitudes of ECoG before and after starting to elicit CSD as the basis for assessing the occurrence of potentiation of spontaneous electrical activity. For each recording amplifier, the gain was kept constant throughout the record. The remaining 5 W rats of the ECoG study constituted one additional control group, designated as CSD^{-}. This control group consisted of rats in which CSD was not elicited at all and served to test whether the time of recording could influence changes in the ECoG amplitudes. During the recording period, rectal temperature was maintained at 37 ± 1°C by means of a heating pad.

The ECoG and the slow potential changes of CSD were amplified by connecting the electrodes to GRASS DC

amplifiers, and the ECoG was recorded with AC amplification (bandpass filters set to the 1–35 Hz range). The recordings were performed in a model 7-D GRASS chart paper recorder. From each animal, four ECoG samples of about 10 min of the ink-writer recordings were scanned on an HP scanner (model Scanjet-4890) with a resolution of 300 dpi. Two of these samples were taken during the baseline period (before CSD) and a further two samples came from the post-CSD period. The algorithm for processing the images was implemented in MATLAB™. Processing included image binarization, salt-and-pepper–like noise filtering, pixel to vector conversion, and high-frequency signal filtering (Bruce 2000). Following this processing, two vectors were extracted from the binarized ECoG image for each column of pixels, representing the amplitude of the signal. The algorithm for vector extraction searches the data from the first pixel (bottom left) to the last one (top right). These vectors form the envelopes of the ECoG activity, and the mean difference between them determines the amplitude variation of the ECoG. The pixel values for before and after CSD were then normalized, with a unitary value assigned to the lowest amplitude.

For the recording of the transcallosal cortical evoked responses, 5 W and 5 M rats were studied. In these animals, a metallic bipolar concentric stimulating electrode (1-mm distance separating the tips) was positioned in the left parietal cortex (1 mm deep). Through this electrode, stimulating pulses (2 V; 0.3 ms; 0.5 Hz) were applied. A borosilicate glass recording micropipette (10-µm tip diameter) filled with 2 M NaCl was inserted into the homologous region of the right cortex to record the field potential responses evoked by the contralateral electrical stimulation. The evoked responses were amplified, filtered at 3 kHz, digitalized through an analog-to-digital converter (DIGIDATA 1322, Axon Instruments Corp.), and stored in an IBM-compatible computer. In each animal, the post-CSD amplitudes were compared with those of the pre-CSD period. At the end of the recording session, the still-anesthetized animals were subjected to euthanasia by bulbar injury (provoked by introducing a sharp needle into the cisterna magna), with subsequent cardio-respiratory arrest.

The intergroup weight differences were compared using *t* tests. Intragroup amplitude differences in the spontaneous and evoked cortical activity, before versus after CSD, were analyzed with paired t tests. Differences were considered significant when $P < 0.05$.

Results

As shown in the upper panels of Fig. 1, malnutrition during the suckling period (group M) resulted in lower ($P < 0.05$) body weights from postnatal days 14–90, with an average

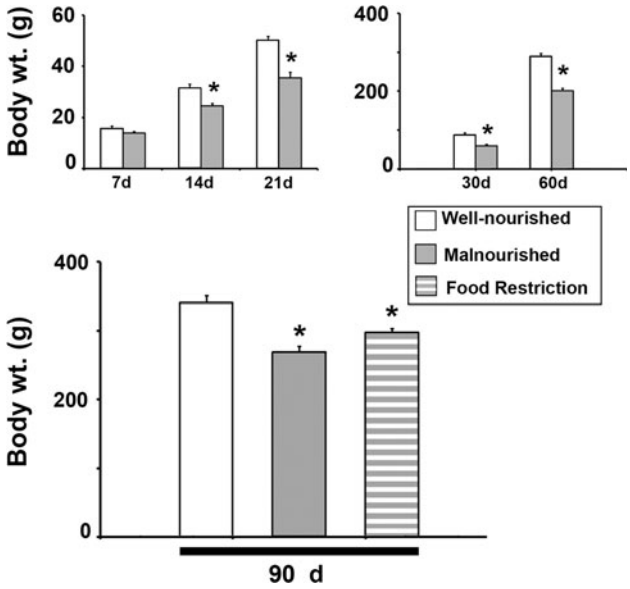

Fig. 1 Body weight (mean ± standard error of the mean) of the well-nourished (W; $n = 10$; litters formed by 6 pups), malnourished (M; $n = 10$; litters formed by 12 pups), and food-restricted rats (FR; $n = 7$; 30% diet restriction for 21 days in adulthood). Weights were measured on days 7, 14, 21, 30, 60, and 90. In the FR group (*lower panel*), the weight was measured only at 90 days of age. The *asterisks* indicate the M and FR values that are significantly lower from the corresponding W controls ($P < 0.05$, unpaired *t* tests)

weight reduction of 27.3 ± 4.5% as compared to the W control group. The FR group (restricted at adulthood during 21 days by receiving only 70% of the daily food consumed by the age-matched controls) also presented a significant (13.4 ± 3.6%) weight reduction at the end of the restriction period (at 90 days of age; Fig. 1, lower panel).

Figure 2 shows representative electrocorticogram recordings of 4 rats, respectively, from the W, M, FR, and CSD^- groups. In the three groups that underwent CSD (W, M, and FR), an increase in ECoG amplitude could be noted after the CSD episodes began to be elicited in the final 2-h period of the recording (right column), as compared with the initial (baseline) 2-h period (left column). In the CSD^- group, no CSD was elicited and no amplitude increase could be detected.

Figure 3 presents the quantification of this CSD-related potentiation effect. Compared with the baseline recordings (2 initial hours), the ECoG amplitudes in the CSD period (2 final recording hours) increased significantly ($P < 0.05$; paired *t* test) for the W, M, and FR groups at recording point *a* (mean increases of 22, 23, and 13%, respectively). In point p, the amplitude increase was significant in group M only (a mean increase of 22%). The intragroup statistical analysis between amplitude potentiation at the anterior versus posterior recording points revealed that the potentiation

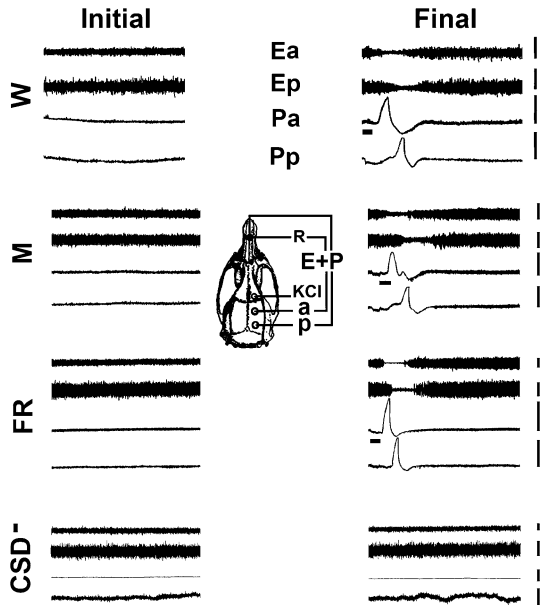

Fig. 2 Examples of recordings of spontaneous cortical activity. Electrocorticogram (E) and DC potential recordings (P) on the right hemisphere of four animals from three groups in which CSD was elicited at the final 2 h of the recording period (well-nourished [W], malnourished [M], and food-restricted [FR]) and another W control group in which CSD was not elicited (CSD^-). The inset shows the anterior (*a*) and posterior (*p*) recording positions, from which the traces marked at the center with the same letters were obtained. The positions of the common reference electrode (*R*) and the application place of stimulus (KCl) are also shown. The *horizontal bars* in Pa-traces indicate the period (1 min) in which stimulation with 2% KCl was applied to the frontal region of the same hemisphere to elicit CSD. Vertical bars correspond to −10 mV in P and −1 mV in E (*negative upwards*). For all groups, the left traces refer to the 2-h initial period (*baseline period*), and the right traces refer to the 2-h final period (in which CSD was elicited). In the three CSD groups (M, W, and FR), an increase in the ECoG amplitude can be observed in the final (*right traces*), as compared with the baseline ECoG (initial; *left traces*) for the same animals. In the CSD-free group (CSD^-), no amplitude increase could be seen. Final excerpted traces in the W, M, and FR groups were taken at the following temporal intervals (t) after beginning CSD elicitation: W-group, $t = 20$ min (traces show the second CSD elicitation); M group, $t = 60$ min (traces show the fourth CSD elicitation); FR group, $t = 60$ min (traces show the fourth CSD elicitation). In the CSD-group, the "final" traces were taken 120 min after the "initial" traces

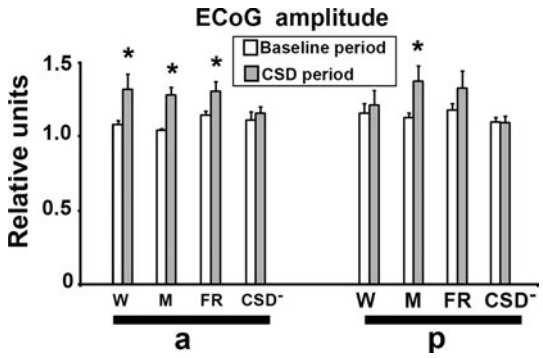

Fig. 3 ECoG amplitudes in adult rats that were well nourished (W; $n = 10$), early malnourished (M; $n = 10$), or food restricted in adulthood (FR; $n = 7$). Data are presented as mean ± SEM relative units (values of the digitalized amplitudes normalized in relation to the lowest value, which was considered equal to 1). Compared with the baseline period (*white bars*), the amplitudes after CSD (*gray bars*) are significantly higher ($P < 0.05$; paired *t* tests) in all nutritional groups at the anterior point (*a*), as indicated by the *asterisks*. At the posterior recording point (*p*), the amplitude increase is significant only in the M group. Intragroup statistical comparison of amplitude potentiation in the anterior versus posterior recording points indicated that the potentiation effect in point p was comparable to that in point *a* only in the M group ($P < 0.05$; unpaired *t* test). In a fourth well-nourished control group, in which no CSD was elicited (CSD^-; $n = 5$), no amplitude increase was seen

effect in point p was comparable to that in point *a* only in the M group ($P < 0.05$; unpaired *t* test). No amplitude difference could be observed through the four recording hours in the CSD-free control group (CSD^-).

The transcallosal cortical responses evoked by electrical stimulation also presented post-CSD increases in amplitude when compared with the pre-CSD values for the same animals. The recordings shown in the upper panels of Fig. 4 are examples of these amplitude increases, which on average were 21.5 ± 9.6% and 41.8 ± 28.5% for the W and M groups, respectively ($P < 0.01$; lower panel of Fig. 4).

Discussion

In this study, we identified in vivo CSD-related amplification in the electrophysiological cortical spontaneous and evoked activities in adult rats subjected to different nutritional conditions. The data demonstrate that CSD triggered by application of KCl induced a potentiation of the amplitudes of the ECoG and of the transcallosal evoked responses that nutritional status seemed to modify in a regional manner. To the best of our knowledge, the present data provide the first in vivo demonstration of ECoG amplitude potentiation associated with CSD in the rat cerebral cortex. The finding that the ECoG activity is actually potentiated by CSD, and not by the duration of the ECoG recording, is in line with the suggestion that CSD could be related to the LTP phenomenon (Footitt and Newberry 1998). Thus, we discuss the underlying mechanisms of this CSD effect in light of the evidence supporting the CSD—brain excitability relationship.

It appears that the potentiation effect described here is similar to that previously reported in vitro in rat cortical slices (Footitt and Newberry 1998), in the rat spinal cord (Gorji et al. 2004), and in vivo in electrically evoked responses in the frog optic tectum (Guedes et al. 2005). We suggest that post-CSD potentiation probably is a general feature of the nervous tissue, involving mechanisms common to brain spontaneous and evoked electrical activity. It

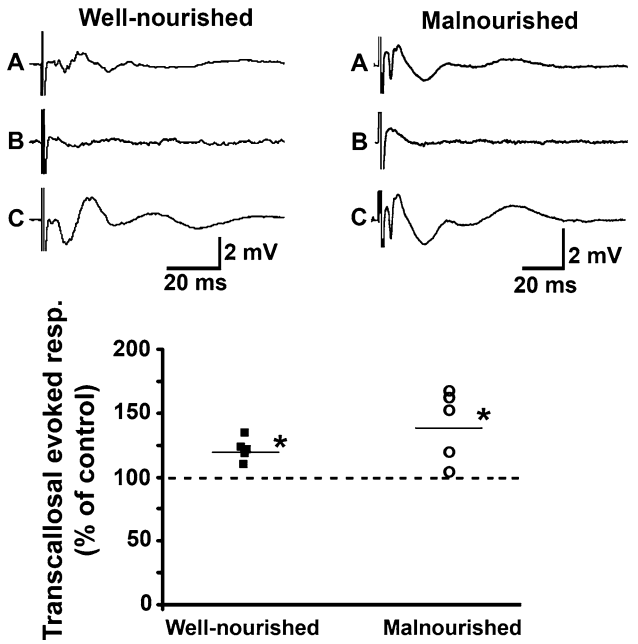

Fig. 4 Recording of electrically elicited transcallosal evoked responses, recorded in the parietal cortex of one well-nourished (W) and one early-malnourished (M) rat. Electric stimulation (2 V; 0.3 ms; 0.5 Hz) was carried out in the left parietal cortex, and the evoked response was recorded on the homologous point of the right cortex. The *upper panels* show averages of 20 consecutive responses recorded before (*A*), during (*B*), and 45 min after CSD (*C*) in one W and one M rat. Increases in the post-CSD evoked responses can be seen in C, as compared with A. Suppression of the responses during CSD is evident in B. The *lower panel* shows the quantification of this effect in five W and five M rats. The *asterisks* indicate significant ($P < 0.01$; paired *t* tests) post-CSD increases in the amplitude of the evoked response in the W and M groups (respectively $21.5 \pm 9.6\%$ and $41.8 \pm 28.5\%$), as compared with the pre-CSD values

is also common to lower vertebrates and mammals, and not a particular characteristic of a single species. In addition, a similar potentiation response associated with CSD has been described in human cortical tissue in vitro (Gorji and Speckmann 2004). Because we found no potentiation in the CSD-free group (CSD^-), we suggest that the CSD-induced amplitude enhancement is not an event that depends on the time elapsed since the beginning of the recording, but rather a real synaptic change induced by CSD, as recently suggested (Faraguna et al. 2010). Thus, our in vivo data reinforce the idea of a CSD-induced LTP-like phenomenon (Footitt and Newberry 1998; Guedes et al. 2005). In this context, it is interesting to mention that LTP may also be induced in vitro by brief exposure to KCl (Bernard et al. 1994), a stimulus that can also trigger a CSD. The induction of an LTP-like phenomenon by CSD receives support from experimental evidence. Indeed, CSD can elicit long-lasting depolarization of neurons and also can activate NMDA channels, producing increases in extracellular potassium and intracellular calcium (Somjen et al. 1992).

Two distinct mechanisms could account for the present CSD effect. First, considering that the action of excitatory amino acids is an important source of brain excitatory influences (Hicks and Conti 1996), it is reasonable to suggest the involvement of NMDA-linked mechanisms in the CSD potentiation effect. Second, it is also conceivable that the participation of disinhibition mechanisms, acting on feed-forward inhibitory synapses (McMahon and Kauer 1997), could be involved. In fact, these two mechanisms may not necessarily be mutually exclusive, but rather could act together, an idea that requires further investigation.

In line with previous studies (Rocha-de-Melo et al. 2006; Rich et al. 2010), we were effective in inducing malnutrition, as judged by the weight reduction found in the M and FR groups. Nutritional deficiency can contribute to effects on basic neural functions such as sensory information and sensation perception processing, as well as execution of motor tasks (Barret and Radke-Yarrow 1985). Malnutrition can also impair more elaborated functions such as those involving consciousness, cognition, learning, memory, and emotion, and electrophysiological evidence points to excitability-related disturbances resulting from malnutrition (Almeida et al. 2002). As a consequence, the organism may become more susceptible to certain neurological disorders, such as epilepsy (Morgane et al. 1978; Almeida et al. 2002; Florian and Nunes 2010). The recording of evoked and spontaneous brain electrical activity has been previously used to investigate to what extent nutritional disorders affect electrophysiological aspects of the brain (Morgane et al. 1978; Guedes 2005). Early malnutrition, but not food restriction at adulthood (group FR), was shown in the current work to enhance ECoG potentiation associated with CSD in the posterior recording region, suggesting a nutrition-related modification of the potentiation effect at this posterior region. Because this modulation did not occur in the group undergoing food restriction in adulthood, we suggest a development-dependent action of malnutrition, which would reflect plastic modifications of neural function (Cheetham and Finnerty 2007). The mechanisms by which nutritional deficiency disrupts brain development and function seem to include processes like dendritic development, synapse formation, and myelination (Morgane et al. 1978; Picanço-Diniz et al. 1998). As previously demonstrated, malnutrition can impair gliogenesis and myelin formation and increase brain cell packing density (Morgane et al. 1978). When compared with the normal brain, the early-malnourished brain is smaller than normal, with smaller cells that are packed more densely and have reduced myelin. Under such conditions, CSD has been shown to be facilitated (Frazão et al. 2008). In nutritionally normal animals, impairment of glial function (Largo et al. 1997) and of myelination (Merkler et al. 2009) also favors CSD propagation, while overnutrition (Rocha-de-Melo

et al. 2006) and hypermyelination (Merkler et al. 2009) impair it. Malnourished rats present an increase in brain levels of glutamic acid decarboxylase (Díaz-Cintra et al. 2007) and decreased brain glutamate uptake (Feoli et al. 2006); two conditions that can lead to an increase in extracellular glutamate, which also would facilitate CSD and may have contributed to the post-CSD potentiation of the evoked and spontaneous cortical activity.

Concerning the ECoG effect, our data on the CSD-related potentiation in the well-nourished rats indicated regional differences in the cerebral cortex, with the anterior recording region being more susceptible to the CSD potentiation as compared to the posterior location. Early malnutrition seemed to modify this response pattern, enhancing the susceptibility of the posterior recording region to this effect. We are currently unable to explain the molecular mechanisms for why malnutrition would modify the response pattern to CSD in a regional manner, resulting in regional differences in ECoG potentiation. One possibility to be further explored would be based on the malnutrition-induced disruption of the cortical gradient of neuronal cell packing density (Soto-Moyano et al. 1999). However, we believe that generating this kind of data would help in understanding the link between malnutrition and brain regional difference in electrophysiological responses at structural, biochemical, and molecular levels. We know from the literature that distinct brain regions can react differently to nutritional and pharmacological challenges. For example, regional brain differences have been previously reported under specific nutrient deficiency (Miyazawa et al. 2010). Also, regional response differences in the rat cortex have been recently described for differential effects of anti-migraine drugs on CSD (Bogdanov et al. 2011), as well as for neurovascular coupling, via functional magnetic resonance imaging and electrophysiological recording (Sloan et al. 2010). Regarding the relevance of our findings for the human brain, it is interesting to consider the recent report of regional differences in EEG functional connectivity in extremely low-birth-weight infants as compared to term infants (Grieve et al. 2008).

In conclusion, the present in vivo study documents a novel electrophysiological action of CSD on spontaneous and evoked cortical electric activity in well-nourished and early-malnourished rats, allowing us to draw three conclusions. First, after CSD elicitation in the rat cortex, the spontaneous and evoked activities increase their amplitudes. Second, regarding the ECoG, the parietal anterior region is more susceptible to this CSD action than the parietal posterior area, suggesting regional differences. Finally, malnutrition early in life enhances this potentiation in the parietal posterior recording region, suggesting a nutrition-related imbalance between cortical excitation and inhibition mechanisms that modulates brain excitability in a regional manner. Considering that evidence is available associating CSD mechanisms and processes underlying excitability-related human disorders like migraine (Goadsby 2006; Moskowitz 2007) and epilepsy (Guedes et al. 1992; Guedes and Cavalheiro 1997; Berger et al. 2008), the present data might advance understanding of the CSD/brain excitability/nutrition relationship in the developing brain.

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Conflict of interest None declared.

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