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Early Life Seizures and Their Long-term Impacts on Cognition: The Role of Synaptic Plasticity Dysfunctions as an Underlying Mechanism

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ABSTRACT

Objective: Symptomatic seizures are frequent events during childhood. Previous studies indicate a relationship between these events and the onset of an epileptic condition. However long-term effects of seizures on neurocognitive function remain poorly understood. Our objective is to develop a conceptual framework linking key clinical and experimental findings with electrophysiological studies attempting to elucidate the mechanisms involved with early life seizures (ELS) outcome. **Methods:** In this review clinical and experimental studies were addressed to raise the main findings of the literature on ELS long-term consequences. To better understand the neural substrates of cognitive outcome of ELS we have reviewed electrophysiological studies in animals that addressed experimental forms of synaptic plasticity such as long-term potentiation, long-term depression and paired pulse facilitation (LTP, LTD and PPF) and oscillatory patterns in the hippocampus and the prefrontal cortex (PFC) that relate to behavioral and molecular alterations after ELS. **Results and conclusions:** Evidences from literature indicate that the immature brain may be not as resistant to seizure effects as previously thought. ELS increase hippocampal excitability, enhance the vulnerability to seizures in the adult, and modify the expression of GABA and glutamate receptors. Moreover ELS induce changes in h-channels and CB1 cannabinoid receptors. Frequent seizures during development produce impairment in learning and memory tasks, which relates to LTP impairment and LTD facilitation in the hippocampus. Apparently, frequent ELS could disrupt the molecular mechanisms implicated in synaptic plasticity induction. Studies also indicate the PFC as a key brain region involved in the behavioral and cognitive alterations of ELS. Future studies on ELS could evaluate a broader set of limbic regions and their plasticity mechanisms, contributing to a better understanding on psychiatric comorbidities of the epilepsies.

Keywords: early life seizures; synaptic plasticity; temporal lobe epilepsy; learning, memory; hippocampus; prefrontal cortex.

RESUMO

Crises na infância e o impacto a longo prazo sobre a cognição: o papel das disfunções da plasticidade sináptica como um mecanismo subjacente

Objetivo: Crises sintomáticas são eventos frequentes durante a infância. Estudos apontam para uma relação entre estes eventos e o início de uma condição epiléptica. Entretanto os efeitos de longo prazo das crises nas funções cognitivas permanecem pouco compreendidos. Nosso objetivo é desenvolver um arcabouço conceitual relacionando os principais achados clínicos e experimentais com estudos eletrofisiológicos na tentativa de elucidar os mecanismos envolvidos com as consequências das crises epilépticas durante a infância (CEDI). **Métodos:** Nessa revisão estudos clínicos e experimentais foram abordados levantando-se os principais achados da literatura sobre a evolução das CEDI. Para uma melhor compreensão dos substratos neurais envolvidos nos prejuízos cognitivos causados por CEDI nós revisamos estudos eletrofisiológicos em animais que investigaram formas experimentais de plasticidade sináptica como potenciação de longa duração, depressão de longa duração e

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facilitação por pulso pareado (LTP, LTD e PPF) e padrões oscilatórios no hipocampo e córtex pré-frontal (CPF) que se relacionam com alterações comportamentais e moleculares após CEDI. **Resultados e conclusões:** Evidências da literatura indicam que o cérebro imaturo pode não ser tão resistente aos efeitos das crises como se pensava anteriormente. CEDI aumentam a excitabilidade hipocampal, aumentam a vulnerabilidade a crises no adulto, e modificam a expressão de receptores GABA e glutamato. Além do mais CEDI induzem mudanças em canais-h e receptores canabinóides CB1. Crises frequentes durante o desenvolvimento produzem prejuízo em tarefas de aprendizado e memória que se relacionam a diminuição da LTP e facilitação da LTD no hipocampo. Aparentemente, CEDI frequentes podem interferir com os mecanismos moleculares implicados na indução de plasticidade sináptica. Estudos também indicam o CPF como uma região cerebral criticamente envolvida nas alterações comportamentais e cognitivas da CEDI. Estudos futuros em CEDI poderiam avaliar um conjunto mais amplo de regiões límbicas e seus mecanismos plásticos, contribuindo para um melhor entendimento das comorbidades psiquiátricas das epilepsias.

Unitermos: crise na infância; plasticidade sináptica; epilepsia do lobo temporal; aprendizado; memória; hipocampo; córtex pré-frontal.

INTRODUCTION

Epileptic seizures are the most common neurological emergency in childhood, affecting approximately 2-5% of children up to 5 years old[1-3]. Among them, febrile seizures are the most frequent and can be divided into complex and simple[1]. Complex febrile seizures are characterized by a prolonged duration (>15min), focal seizure onset or recurrent seizure within 24h. Simple febrile seizures, which make up 75% of the attacks, do not present these features[2]. There is controversy whether these prolonged seizures can initiate a pathophysiologic process that would culminate in mesial temporal sclerosis[1]. Besides the frequent history of a complex seizure in patients with epilepsy, only a small amount of the population who suffered ELS develops subsequent epilepsy[2,4]. Also experimental studies have shown that immature rats do not present the classical neuronal loss and cell damage after episodes of provoked seizures found in adult animals[2,5-8]. The aforementioned evidences contribute to the idea that the immature brain is more susceptible to seizure induction, although is more resistant to its consequences. However, recent experimental data have shown changes in molecular and neurotransmitter receptor expression possibly leading to enhanced hyperexcitation as a consequence of ELS[9-12]. Also, there is controversy whether the ELS may have other neurological consequences such as cognitive impairment. Recent experimental findings have demonstrated the impact of ELS in hippocampal synaptic plasticity as a possible substrate of epileptogenic changes and cognitive deficits[1,13,14]. A number of studies have connected neural plasticity with the pathophysiology of mental disorders like epilepsy, mood disorders and schizophrenia[15-18]. Current theories hypothesize that neuroplastic alterations during development may contribute to structural and functional changes in important circuits, which can drive long-lasting effects on adult brain function[15,19].

HUMAN STUDIES

The International League Against Epilepsy (ILAE) Commission on Classification and Terminology has recently revised concepts, terminologies, and approaches for classifying seizures and forms of epilepsy[20]. One of the issues included was the abandonment of the designation "benign" epilepsies in childhood epilepsy. The argument against the term "benign" is based on a misleading interpretation of its consequences, which usually implies "no sequels left" to the patients and that has been recently challenged[21].

Epidemiological studies have shown that the incidence of epilepsy is highest in early childhood; it is three-times higher in the first year of life than in mid-adulthood[3]. The course of seizure disorders in infancy and childhood ranges from transient to life-long, depending on the epilepsy syndrome, causes, and possibly treatment. The natural history of some epileptic syndromes may be time-limited; others might relapse, and others might persist into adulthood[4,22]; and frequency of clinical seizures may not be directly associated with the severity of cognitive impairment[23,24].

Regarding, the relationship between early-life seizures (ELS) and the subsequent development of epilepsy or other long-term sequels remains highly controversial. Retrospective studies indicate that adults with temporal lobe epilepsy (TLE) frequently report having experienced childhood febrile or non-febrile status epilepticus (SE; defined as 30min of continuous epileptic seizure activity or two or more sequential seizures without full recovery of consciousness between seizures), which makes ELS a potential risk factor for the later development of epilepsy[4]. It also has been suggested that ELS may lead to long-term cognitive and social interaction impairments and might be associated with the progression of mesial temporal sclerosis[4,22]. Moreover, it is not yet known whether ELS result in either permanent hippocampal damage or altered levels of excitation and inhibition that could be

predisposing factors for spontaneous seizures later in life. Animal models of ELS can eliminate factors such as prior brain injury, medication effects, and behavioral interactions that also impact learning ability. There is a body of evidence in rodents showing that ELS impact learning and memory in adulthood[25], which are associated with aberrant mossy fiber sprouting in the CA3 region, increased neurogenesis in the dentate gyrus, alterations of glutamate and GABA receptor expression and enhanced hippocampal excitability[25-27].

ANIMAL MODELS

Several experimental protocols were developed to model seizures during development aiming to elucidate the epileptogenic mechanisms[28]. In ELS models, seizures are induced in rodents at postnatal age less than 20 days old (<P20). Then, behavioral changes and susceptibility to further seizures are probed in the same animals in the adulthood. ELS have been studied by febrile seizures induction (increasing body temperature), SE induced by pharmacological stimulation with pilocarpine alone or combined with lithium (LI-PILO), kainic acid or pentylenetetrazol (PTZ), repeated convulsive seizures induced by flurothyl, and models of hypoxia[2,6,29].

ELS animal models do not exhibit the classical neuropathological findings of temporal lobe epilepsy (TLE) or those associated with SE in adult animals[2,5-8]. Despite the lower threshold for generation of seizures in immature brains, developing animals are less vulnerable, in terms of damage and neuron loss than mature animals to a wide range of insults[6]. The behavioral consequences following SE are also dependent on the age of the animal by the time of SE. Adult animals submitted to ELS have higher mortality rate, significant memory, learning and behavioral impairments[30,31], neuronal loss and subtle neuronal plasticity[6,32-36]. Likewise, spontaneous seizures are more likely to occur in adults who experienced SE than in young animals[6]. Younger rats (<P18) usually do not develop convulsive spontaneous seizures as a late consequence of SE[37]. However, 90-120 days after ELS they show electrographic and behavioral alterations similar to those observed in rodent models of genetic absence epilepsy[37,38]. In addition, animals subjected to multiple SE at P7 to P9 express several electroencephalographic disturbances[39]; though rarely develop convulsive seizures or neuronal loss in limbic and neocortical structures[38]. Several studies have also demonstrated that the immature brain (P10-P12) when exposed to febrile convulsions, but not followed by spontaneous seizures, are associated to hippocampal hyperexcitability in the adult[9,10]. Therefore, the relationship between electrographic seizures and cognitive deficits in models of ELS is an important field to further investigations.

Animal models of febrile seizures are considered particularly important, because fever is the most prevalent cause of seizures in children[2,4]. Experimental febrile seizures can be evoked in young rats at an age when the developing hippocampus is equivalent to those of human patients[40]. In immature rats it was observed that hyperthermia causes seizures in almost all subjects, suggesting that genetic susceptibility is not a prerequisite for their generation[41]. Prolonged febrile seizures (~20min) in young rats produced changes in the cytoskeleton of hippocampal neurons that persists throughout weeks[42]. Using magnetic resonance imaging (MRI), 75% and 85% of animals have shown abnormal T2 signal in the hippocampus, piriform cortex and amygdala, 24h and 48h after febrile seizures, respectively[43]. However, there was no cell death or neuronal injury suggesting that these changes are reversible[43]. Despite the absence of pathological findings, adult animals submitted to febrile seizures during development have an increased excitability of hippocampal circuitry, increased susceptibility to induction of new and recurrent spontaneous seizures in a small amount of these animals[44]. The underlying changes associated with increased hyperexcitability involve lasting changes at molecular and functional levels, including changes in h-channels and CB1 cannabinoid receptors on GABAergic interneurons of the hippocampus[11,12,45]. Additionally, several studies indicate that hyperthermia-induced seizures promote changes in programs of gene expression of numerous molecules that regulate neuronal excitability and response of the neural network[41]. Altogether, the aforementioned data indicate that the immature rat brain may be not as resistant to SE-induced damage as previously thought, but probably more susceptible to activity-dependent plasticity leading to cognitive deficits associated to molecular and network reorganization underlying hippocampal hyperexcitability[46,47].

COGNITIVE DEFICITS

ELS are often associated with neurological dysfunctions that may persist in adults[48,49]. In fact, the IQ of children with epilepsy tends to be lower compared with children without epilepsia[50,51] and the number of children with learning difficulties is higher than in the general population[52-55]. Although the diversity of factors that may contribute to cognitive impairment – age of onset of seizures, etiology, genetics and drug treatment – clinical reports and laboratory evidence indicates that the recurrence of seizures has an important role in cognitive impairments[49].

Findings on cognitive development in patients who experienced recurrent febrile seizures are contradictory. Verity and colleagues[56] and Ellenberg and Nelson[57] found no difference in IQ between children with a single febrile

seizure and those with recurrent febrile seizures. However, Kolfen and colleagues report that children with multiple febrile seizures had worst neuropsychological performances than controls or patients with a single seizure caused by fever[58]. Studies in models of repeated ELS indicate cognitive impairment during adolescence or adulthood. After flurothyl recurrent neonatal seizures, the animals showed impaired spatial memory[49,59,60]. Similarly, repeated seizures caused by PTZ[61] and hipertermia in rats[13] during development resulted in impairment on tests of spatial memory.

The cellular and molecular mechanisms of long-standing cognitive impairment after ELS are still unclear. It is possible that sprouting of dentate mossy fibers following ELS is involved in the learning and memory deficits observed in the step-down inhibitory avoidance task[25]. In a recent study, it has been reported a negative correlation between the latency to the step down in the test phase and the score for mossy fiber sprouting in Li-PILO-treated animals[25]. However, some studies were unable to identify specific histological changes in the hippocampus that are critical predictors for the development of epilepsy after ELS[62]. Hence, changes at a cellular or molecular level, such as abnormalities in neuronal cytoarchitecture, neurotransmitter receptors subunits, voltage-gated channels or structural changes occurring outside the hippocampus may be critical mediators of epileptogenesis in the developing brain[63,64]. In addition, some studies have indicated that the abnormal electrical activity associated with SE in neonatal rats can lead to life-long changes in the expression of glutamate receptors subunits and its transporters[65,66]. The mechanisms responsible for the deficits associated with the seizures during development are still not clear, but synaptic plasticity dysfunctions in the hippocampus and extra-temporal networks are possible substrates of cognitive impairments.

SYNAPTIC PLASTICITY

The continuum between plasticity and pathology is a hypothesis supported by electrophysiological and molecular studies[67]. Synaptic efficiency is regulated according to a dynamic balance between excitation and inhibition[67]. It is suggested that in pathological conditions, the balance between excitation and inhibition would be disrupted, resulting in a tendency toward hyperexcitability and hypersynchrony[67,68]. Consistently, long-term potentiation (a cellular model of memory; LTP) and kindling share similar mechanisms, such as the need for high-frequency stimulation, glutamatergic neurotransmission, regulation of intracellular calcium concentration, changes in gene expression, protein synthesis and synapse structure, and activity of metabotropic glutamate receptors[67]. Electrophysiological studies in models of epilepsy have shown that repeated seizures have deleterious effect on hippocampal LTP[69,70]. Recently it was demonstrated a decrease in hippocampal LTP in rats submitted to SE[68]. This effect was correlated with a worsening in spatial memory tasks dependent on the hippocampus. It has been argued that epileptiform discharges can generate saturation of the synaptic response or changes in the molecules associated with the induction of plasticity[68].

SYNAPTIC PLASTICITY IN EXPERIMENTAL ELS

Lynch et al demonstrated that a single seizure caused by kainic acid at different ages (P1, P7 and P14) was able to reduce the induction of LTP in hippocampus slices and increase paired pulse facilitation (a brief form of synaptic plasticity; PPF), which was related to deficits in spatial memory[71]. Similarly, Zhou et al., using hypoxia model of ELS, have found that 48-72h after seizures animals showed attenuation of LTP induced by stimulation of the Schaffer collaterals *in vitro*[72]. In the same animals, increased expression of AMPA receptors and a significant decrease in the incidence of silent synapses were found in the hippocampus[72].

Synaptic plasticity dysfunctions were also reported in febrile seizures models[1]. Animals submitted to frequent febrile ELS showed deficits in hippocampus dependent long-term memory, which was not observed in the animals that were submitted to a single febrile seizure or in control groups[13]. These findings argue that the cognitive deficits are consequences of recurrent febrile seizures. Similar hyperthermia seizures can lead to lasting bidirectional modulation of synaptic plasticity. Using hippocampal slices of developing rats subjected to frequent febrile seizures, Chang et al.[13], observed impaired LTP and enhanced LTD (long term depression) in CA1 neurons. The molecular substrate involved is the transcription factor CREB (cAMP response element binding protein) that mediates nuclear response induced by activity and is involved in the mechanisms of synaptic plasticity[1]. A decrease in CREB phosphorylation (pCREB) was found in the groups submitted to a learning task, although no changes were found in levels of synaptophysin, basal level of pCREB and total CREB level. Moreover, rolipram (phosphodiesterase antagonist) restored the phosphorylation of CREB after learning tasks, reversing these impairments[13]. Thus, ELS can generate behavioral abnormalities primarily related to subtle changes involving receptor expression, intracellular signaling and hippocampal synaptic efficiency in adults animals[1]. However, most of these studies focused on hippocampal modifications and it is unclear how ELS affect more distributed circuits that could contribute both to seizure enhanced susceptibility and a poor cognitive outcome.

ELS AND EXTRA-TEMPORAL CIRCUITS

The investigation of abnormalities in extra-temporal circuits is important as it may help us to understand some behavioral disorders that are commonly associated with ELS including autism, attention-deficit-hyperactive-disorder, obsessive-compulsive disorder and psychosis[73]. These conditions are thought to involve alterations in frontal lobe function, implying that ELS may permanently alter the neurological substrates underlying those behaviors. In this sense, it was recently demonstrated that flurothyl-induced ELS impairs behavioral flexibility as measured by the capacity to shift a lever-preference in an operant chamber with two levers – performance that requires a functional mPFC. Furthermore, the prelimbic mPFC seems to undergo an anatomical change with an increase in thickness particularly restricted to the deeper layers, with no change in cell density. PFC thickness was positively correlated with the acquisition of lever preference (i.e. increased preference implies less flexibility). Such correlation indicates that ELS induced alterations in the PFC, which could contribute to the behavioral flexibility impairments[74]. ELS induced by Li-PILO also impact the neurotransmission in mPFC-associated networks[75]. It was described that behavioural sensitization after repeated administration of methamphetamine in adolescent rats is enhanced if the animals are previously subjected to ELS at P10. In addition, it was demonstrated that Li-PILO ELS affects the prefrontal-striatal circuitry modulating the level of dopamine and glutamate. Particularly, the dopamine turnover was significantly higher in the mPFC of Li-PILO rats as compared controls. Besides, there was a significant increase of glutamate in the mPFC of Li-PILO rats[75]. Altogether, these data indicate that the ELS model generated by Li-PILO treatment at P10 can reproduce some of the characteristic neurochemical changes observed in animal model of psychosis, such as the ketamine model[76].

In one study, the relationship between oscillatory patterns, memory and ELS was investigated in rats that experienced one hundred flurothyl-induced seizures during P15-P30[77]. Animals had LFPs recorded from the prefrontal cortex and hippocampus (CA1 and CA3) during all phases of a delayed-nonmatch-to-sample (DNMS) task. The results indicate that following ELS, the initial performance deficit is followed by a recovery phase, which is associated with the development of distinct patterns of brain oscillations in the hippocampal-PFC network, when compared to control animals. Rats undergoing ELS showed increase in theta and gamma power, both during the acquisition and retrieval phase. ELS rats also demonstrated a parallel increase in PFC theta power together with the increase in difficulty of the DNMS test[77]. An apparent limitation of this model is that, in addition to a normal development towards adulthood following the ELS, adult animals have no epileptiform activity in their electroencephalogram recordings.

CONCLUSIONS

Taken together epidemiological studies show a close relationship between prolonged ELS and the emergence of subsequent epilepsy. However data on other neurological consequences, mainly the ones related to cognitive impairment and learning deficits are still controversial. Experimental studies have shown that seizures during development predispose and increase the response to a second seizure enhancing hippocampal excitability. Interestingly, this occurs without neuronal loss or cell damage involved in TLE. However more subtle changes in the glutamate and GABA receptors as well as h-channels and CB1 receptors expression are observed in ELS models and could underlie the enhanced susceptibility to new provoked seizures. Other evidences demonstrate a strong relationship between the frequency of seizures and impairments in learning and memory tasks. Apparently, recurrent seizures during development affect hippocampal plasticity decreasing LTP and increasing LTD, thus affecting performance on memory tasks. Repeated ELS affect the biochemical machinery involved in LTP, modifying the cAMP cascade response and CREB phosphorylation. This suggests that the ELS alter synaptic plasticity directly affecting proteins involved in the plasticity induction which may underlie the cognitive deficits seen in these models. However more studies are needed to determine the roles of this synaptic plasticity impairment in an epileptogenic set. Furthermore little is known about the mechanisms that lead to these molecular changes. We think that a further elucidation of these mechanisms may improve the clinical ELS outcome. Besides, most of the studies have focused on the hippocampus and little is known about the ELS effects on other brain regions. Experimental evidence has demonstrated that the mPFC is a structure affected in the ELS outcome. Also it is well know the importance of the mPFC to cognitive processes and their involvement with psychiatric disorder. Studies probing plasticity dysfunctions in extra temporal regions such as the prefrontal cortex are of great value to understand the clinical relevant comorbidities related to TLE and ELS.

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