

Rbap48 Could Act as a Candidate Biological Predictor for the Cognition Impairments of Patients with Temporal Lobe Epilepsy: A Hypothesis Based on Recent Molecular Findings

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Abstract

The temporal lobe epilepsy (TLE) is characterized by the neurodegeneration, abnormal reorganization of circuitry, and the loss of functional inhibition in hippocampus regions. Particularly, the declined neurogenesis in hippocampus has emerged as a significant hallmark of TLE. RbAp48, which is initially recognized as a retinoblastoma binding protein, is also identified as a positive regulator of human neurogenesis owing to its ability to regulate the expression of the pluripotency, differentiation, and cell cycle genes in human PSCs. The deficiency of RbAp48 critically contributes to the dentate gyrus (DG) dysfunction and is closely related to age-related memory deficits. Nevertheless, the roles of RbAp48 in the neurogenesis deterioration and memory loss of TLE patients remain to be determined. In view of the linkage between the deficiency of RbAp48 and the TLE-related memory loss, it is reasonable to hypothesize that the expression level of RbAp48 in the hippocampus of the TLE patients might be down regulated in accordance with the reduced neurogenesis. As the neurogenesis exhibits a close relationship with the hippocampal functions like learning and memory, the RbAp48 would possibly act as a candidate biology predictor for the cognition impairments of the TLE patients. This notion might cast insights into the etiology of hippocampus-based memory loss in TLE patients with the potentials of opening up new therapeutic avenues.

Keywords: Temporal lobe epilepsy; Hippocampus; Cognition

Introduction

Temporal lobe epilepsy (TLE) is a common neurological disorder that characterized by the spontaneous recurrent unprovoked seizures, cognition impairments, memory loss and depression [1]. Currently, the precise cause contributes to TLE and the underlying pathological mechanism is not totally clear. Pharmacologic therapy represents the first line of treatment for TLE and is effective in most cases. However, approximately one-third of patients develop intractable seizures that cannot be controlled by a wide variety of anti-convulsive drugs [2]. Recent research found that this disorder is associated with neurodegeneration, abnormal reorganization of the circuitry, and loss of functional inhibition in the hippocampal regions [3-5]. Particularly, the declined neurogenesis in hippocampus has emerged as a significant hallmark of TLE. Research based on the epilepsy patients and animal models have found various kinds of reduced neurogenesis in hippocampus, including the reductions in gamma-amino butyric acid-positive (GABAergic) neurons, disappearance of the calbindin in a substantial fraction of dentate gyrus(DG), and the decreased concentration levels of multiple neurotrophic factors such as BDNF, FGF-2, IGF-1. As the neurogenesis exhibits a close relationship with the hippocampal functions like learning and memory, it is proposed that these changes collectively contribute to the complicated features of the TLE patients [6]. However, the detailed molecular mechanisms underlying the cognition impairments of TLE patients are not completely understood.

The histone-binding protein rbbp4 (RbAp48) is a ubiquitously expressed nuclear protein and associated with various functions including mediating chromatin metabolism and assembly, ras signaling, cytoskeletal reorganization, and modulation of cell proliferation [7-10]. RbAp48 is required for the maintenance of multiple human pluripotent stem cells (PSCs) types, such as neural stem cells (NSCs), embryonic stem cells (ESCs) and embryonal carcinoma cells(ECCs) [11]. Decreased expression of RbAp48 concomitantly reduces the expression of the PSCs -specific genes, which are involved in the regulatory

network of organogenesis, particularly the neurogenesis. Thus RbAp48 is considered as a positive regulator of human neurogenesis owing to its ability to regulate the expression of the pluripotency, differentiation, and cell cycle genes in human PSCs. Moreover, the deficiency of RbAp48 plays a pivotal role in the DG dysfunction and it is closely related to age-related memory deficits [12]. The human hippocampus can be affected by a large variety of very different neurological diseases, of which the epilepsy, acute ischemic stroke, transient global amnesia, and limbic encephalitis are the most common causes [13].

The roles of RbAp48 in the neurogenesis deterioration and the complicating memory loss of TLE patients are left to be determined. No study has so far examined changes in RbAp48 expression as a function of epilepsy severity. Therefore, it is valuable to investigate the expression levels of RbAp48 in the hippocampus of the TLE patients and explore the underlying implications of the possible regulation. It was particularly notable that the cognitive impairments and especially memory disruption are the major complicating features of the TLE and they have been considered as the most problematic comorbidity [14,15]. Patients with a longer duration of refractory TLE would exhibit more severe cognitive impairments. Understanding of the neurobiology of disordered cognition especially the memory loss in epilepsy was accelerated by the development of organized epilepsy surgery

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programs and neuropsychology research [16,17]. However, it remains to be challenging to elucidate the origin of cognitive abnormalities, the progression mold, and most importantly, how to predict and protect the cognitive function of TLE patients. Extensive investigations have focused on the hippocampus to form a conceptual framework of the architecture of diverse memory systems. It is well understood that RbAp48 participates in the age-related DG dysfunction and the expression level decreases in ageing hippocampus of human and mice [12,18]. The deficiency of RbAp48 in the DG has been suspected as the underlying cause of age-related memory deficits. Therefore, the TLE probably result in RbAp48 deficiency and this decline might reflect a preferential vulnerability of memory processes in the hippocampus of TLE patients. Meanwhile, the specific deficiency of RbAp48 in the TLE hippocampus might be associated with the high occurrence of memory disruption in the TLE patients. It is evidenced that maintenance of hippocampal-dependent learning and formation of memories require the continuous addition of newly functional granule cells [19]. From this perspective, the impaired neuronal differentiation of NSCs and the decreased neurogenesis that caused by down-regulated expression of RbAp48 may significantly contribute to the cognitive deficits of TLE hippocampus.

Our Hypothesis

In view of the potential linkage between the RbAp48 deficiency and the memory loss, it is reasonable to hypothesize that the TLE hippocampus might be exposed to a preferential vulnerability of postoperative memory decline. Based on the aforementioned findings, we propose that the expression levels of RbAp48 in the hippocampus of TLE patients might be down regulated in accordance with the reduced neurogenesis. As the neurogenesis exhibits a close relationship with the hippocampal functions like learning and memory, the RbAp48 could possibly act as a candidate predictor for the cognition impairments of the TLE.

Evaluation of the hypothesis

The present hypothesis proposes that the cognitive deterioration in TLE patients might be closely related to the deficiency of RbAp48 in the hippocampus. This notion might cast insights into the etiology of hippocampus-based memory loss in TLE patients with the potential of opening up new therapeutic avenues which are rarely touched on. The hippocampus specimens of TLE patients who are subjective to surgery should be collected for the evaluation of our hypothesis. These patients should be diagnosed by multiple methods, including the high-resolution magnetic resonance imaging (MRI), positron emission tomography (PET), long-term video electroencephalography (EEG), and intra-operative electrocorticography (ECOG) according to the International Classification of Epileptic Seizures by the International League against Epilepsy. Further research should demonstrate the utility of multiple measurements, including the immunohistochemistry, real-time PCR and West blotting to quantify the expression level of RbAp48 in the hippocampus tissues of TLE patients. The expression levels of RbAp48 protein in the hippocampus tissues of these TLE patients should be directly detected by immunohistochemistry examination using an antibody directed against RbAp48. Furthermore, the expression levels of RbAp48 protein in the TLE hippocampus should be quantitatively determined by Western blotting, and the expression levels RbAp48 mRNA should be quantified by real-time PCR. These methods, both individual and in combination, might consistently point to the decreased level of RbAp48 in the hippocampus of TLE patients in comparison with age-matched intact hippocampus.

Furthermore, it had been found that up-regulation of RbAp48 in the DG of aged wild-type mice ameliorated their age-related memory loss, and restored their memory to youthful vigor [12]. So it is a logical next step to test these RbAp48 expression enhancers for therapeutic use against the memory deterioration in TLE animal models, and ultimately in TLE patients.

Discussion and Conclusion

As the disparate response in the chronic stages of TLE, the decreased hippocampus neurogenesis has received considerable attention which sought to elucidate the pathophysiology of this disorder [6]. Both studies on the hippocampus of TLE patients and TLE animal models clearly demonstrate that the DG neurogenesis is substantially down regulated. Several neurotrophic factors, such as FGF-2, IGF-1, BDNF, and GDNF, are considered as the positive regulators of neurogenesis in the hippocampus. The concentrations of these neurotrophic factors are decreased during chronic epilepsy [5,20]. Therefore, it is reasonable to deduce that the dramatically declined neurogenesis during chronic epilepsy might be caused by the decreased levels of the aforementioned neurotrophic factors.

The RbAp48, which is characterized by the component of distinct nucleosome-modifying complexes, is initially identified as a retinoblastoma binding protein [21,22]. It has been found that the RbAp48 plays a pivotal role in maintaining human PSCs pluripotency, and is regarded as a positive regulator of human cell differentiation. Regular expression of RbAp48 can facilitate human PSCs, especially the NSCs maintenance, by promoting or permitting expression of a combination of known pluripotency genes and cell cycle regulators (e.g., NANOG, CCNA2 CCNB1) [11]. The decreased level of neurogenesis is consistent with the disruption of a complex shared network which maintains the differentiation of NSCs by a specific controlling program. In view of the crucial functions of RbAp48, it is possible that the decreased expression of this protein might be at least partially contributes to the neurogenesis disruption. The deficiency of RbAp48, together with other changes in the microenvironment of the TLE hippocampus, might mutually influence the overall declined hippocampus neurogenesis. This novel hypothesis originates from the memory defects of TLE may be instrumental to clarify the underlining pathogenesis mechanism of this disease.

NSCs can retain their latent developmental potential while proliferating rapidly. It was found that NSCs survived even in the chronic epilepsy hippocampus, and produced new cells to the levels similar to the age-matched intact hippocampus [6]. However, TLE hippocampus is associated with considerable (95%) decline in neuronal differentiation of the newly born cells in comparison to the age-matched controls [23]. As the TLE does not interfere with the production of the new cells derived from NSCs, thus reduced expression of RbAp48 would not affect the production or survival of the newly born cells, but it does appear to interfere with the neuronal fate choice decision of these newly generated cells [11]. Therefore, decreased expression of differentiation regulator Rbap48 in the TLE hippocampus may suppress the pluripotency of NSCs by instructing them to remain in an undifferentiated state and/ or to switch into the glial fate, rather than the hippocampus neurons. Either or both of these possibilities can reduce the overall neurogenesis during TLE. Thus radically diminished neurogenesis during TLE may act as a consequence of the dramatic decrease in the neuronal differentiation of the newly born cells.

Deficiency of the RbAp48 is likely to dampen the neuronal differentiation of newly born cells derived from NSCs. Therefore, it might potentially be a target for developing future therapeutic strategy for TLE.

It is possible that the maintenance of certain concentration of RbAp48 as well as other neurotrophic factors that promote neuronal differentiation of newly born cells are beneficial for enhancing neurogenesis in the hippocampus. Some innovative studies have demonstrated that grafting of NSCs appears to be a promising approach for improving hippocampal function [24,25]. Moreover, it was evidenced that grafting of NSCs is efficacious for improving neurogenesis in the aging rat hippocampus [26]. In this context, administration of the exogenous RbAp48 as well as other neurotrophic factors into the epileptic hippocampus may stimulate neurogenesis from endogenous NSCs that survive even in the chronically epileptic hippocampus. Persistence of NSCs during TLE is encouraging for developing strategies that have the ability to facilitate improvements in the NSCs generation, expansion, and differentiation. Considering the blood-brain barrier might be leaky during TLE, subcutaneous or systemic administrations of RbAp48 in combination with other neurotrophic factors appear to be a promising treatment.

In addition to providing a novel target for TLE treatment, RbAp48 may also act as a potential predictor of the postoperative memory outcome. As a substantial part of TLE patients endure a worse memory after epilepsy surgery, the post-operative memory performance is of great importance in deciding a reasonable surgery mode and resection scope. A combination of factors including side of resection, baseline memory performance, extent of hippocampal sclerosis, chronological age, and Wada Test performance all provided information regarding prediction of memory outcome. However, the specific biomarkers that forecast the development of cognitive deficits have not been identified and there are relatively few strategies to identify whether the individual TLE patients is at the risk for postoperative cognitive dysfunction. The pioneering researches which fortunately gain access to the resected TLE hippocampal tissues would be instrumental to testify the exact expression levels of RbAp48. Future refinement of that knowledge over time as informed by the postoperative follow up of the patients with RbAp48 deficiency may identify a candidate biology predictor for postoperative cognition.

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