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Review

Reelin, tau phosphorylation and psychiatric complications in patients with hippocampal sclerosis and structural abnormalities in temporal lobe epilepsy☆

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ABSTRACT

Introduction: Temporal lobe epilepsy (TLE) is the most common adult epileptic syndrome. About 30–70% of those cases have neuropsychiatric complications. More than 10% of patients have TLE because of focal cortical dysplasia (FCD) type IIIa.
Objectives: The objective of this study was to review the evidence of reelin (RELN) deficiency and tau phosphorylation role in the histopathological, neuropsychiatric, and hyperexcitability features in TLE because of dysplasia type IIIa.
Methods: The current literature was reviewed using Cochrane, EMBASE, PROSPERO, MEDLINE, and PubMed from 1995 to July 2018. Articles of interest were reviewed by one investigator (RAM).
Results: Reelin deficit is related to an abnormal migration of neurons in dentate gyrus, and its deficit causes dentate gyrus abnormalities, which in turn has been associated with memory deficits in patients with TLE. A decreased in the expression of RELN ribonucleic acid (RNA) was found in patients with TLE and dysplasia type IIIa compared with patients with TLE and isolated hippocampal sclerosis (HS). Reelin might affect the distribution and dynamic instability of microtubules within neurons in the cerebral cortex and their phosphorylation. Amyloid pathology, tauopathy, or phosphorylated tau (p-tau) overexpression has been reported in epileptic human brain and in animal models of epilepsy.
Conclusion: Reelin deficit may determine an abnormal cortical lamination and dentate gyrus dispersion and might be associated with an abnormal tau phosphorylation. These processes can be associated with an abnormal hyperexcitability, neuropsychiatric complications, and a myriad of typical histopathological features seen in patients with TLE because of dysplasia type IIIa.

1. Introduction

Acquired epilepsy is one of the most common chronic neurological diseases affecting approximately 50 millions of people worldwide [1]. Among epileptic syndromes, temporal lobe epilepsy (TLE) is, by far, the most common in adults. Focal cortical dysplasia (FCD) type Ia, Ib, or Ic associated with hippocampal sclerosis (HS) is found in approximately 10% of the patients with TLE, and this association is called FCD type IIIa. Neuropsychiatric disorders, such as psychosis, depression, and memory impairment, have been reported in about 30–70% of patients with TLE [2]. These complications have significant negative impacts on the patient's quality of life [3].

Important cytoarchitectonic changes have been described in brain specimens of patients with TLE caused by FCD type IIIa with and without psychiatric complications and memory deficits [4]. These abnormalities include but are not limited to a loss of layers 2 or 4, hypertrophic neurons

Abbreviations: p-tau, phosphorylated tau; RELN, reelin; TLE, temporal lobe epilepsy; FCD, focal cortical dysplasia; TLS, temporal lobe sclerosis; GCD, granular cell dispersion of dentate gyrus; CR, *Cajal–Retzius* cells; HS, hippocampal sclerosis; MTLE, mesial temporal lobe epilepsy; EAK, ethanolamine kinase; GCL, granule cell layer; GSK, glycogen synthase kinase-3β; ApoER2, apolipoprotein E receptor 2; VLDLR, very low density lipoprotein receptor; PKB, protein kinase B; Src/Fyn, family of tyrosine kinases; Crk/C3G/Rap1, creatine kinase/guanine nucleotide exchange factor (GEF) for Rap1/Ras-proximate-1 or Ras-related protein 1 (small GTPase); SFK/Fyn/CrK, Src family kinase/Fyn family kinase/creatine kinase; SOCS family, suppressor of cytokine signaling; EKR, extracellular signal-regulated kinases; MEK, Mitogen-activated protein kinase; RAF, Rapidly accelerated fibrosarcoma is a serine/threonine-specific protein kinases; BAD, Bcl-2-associated death promoter; MFS, mossy fiber sprouting; MAP2, microtubule-associated protein; MAP1A, microtubule-associated protein; P38, mitogen-activated protein kinases; CDK5, cell division protein kinase 5; MYO1E, myosin-Ie is a protein that in humans is encoded by the MYO1E gene; LAMB1, laminin subunit beta; TUBG1, tubulin, gamma 1 protein; CSNK2A1, casein kinase II subunit alpha enzyme; TUBD1, tubulin, delta 1 protein.

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outside layer 5, accumulation of neurofilaments (NF), temporal lobe sclerosis (TLS), heterotopic neurons in subcortical white matter, small "lentiform" heterotopias, gliosis, granule cell dispersion (GCD) of dentate gyrus, neurons lost in hippocampal regions, abnormal phosphorylation of tau (p-tau), and a site specific distribution of tau phosphorylated within the temporal lobe [4,5]. To date, there are no specific explanation for these cytoarchitectural changes and specific pharmaceutical interventions targeting these comorbidities. This phenomenon is partially explained, because the subjacent mechanism of pathological remodeling remains overall unknown.

Blümcke et al. found a strong correlation between the number of persistent *Cajal–Retzius* (CR) cells and the clinical history of febrile seizure in TLE. According to their results, a particular high number of CR cells were present in patients with early complex febrile seizures. The majority of patients with TLE because of dyplasia type IIIa have history of febrile seizures. These data would indicate that this population of interneurons may play a major role in the pathogenesis of FCD type IIIa. As the CR cells are the main source of reelin (RELN) in central nervous system (CNS), we can think that an alteration in the RELN molecular pathway might be related to the pathogenesis of TLE because of FCD type IIIa [6].

Reelin has been implicated in GCD in patients with mesial temporal lobe epilepsy (MTLE) and in a mouse model of TLE [7]. Reelin participates in cortical lamination, final position of neuroblasts, and plays a major role in the cytoarchitectonic guidance of migrating glia and/or neurons towards their anatomical destination [8]. Also, RELN, throughout its canonical pathway, might affect the distribution and dynamic instability of microtubules within neurons in the cerebral cortex and prevents tau phosphorylation (p-tau) [9].

Recently, an association between tau pathology localized at certain part of mesiotemporal structures and memory deficits and psychiatric complications was reported in patients with TLE [10]. These results indicate that normal learning function and behavior require a fine balance between stability and instability in microtubules in certain part of temporal lobe structures.

Because of the increased evidence of the pathogenic role of p-tau in Alzheimer's disease (AD), other tauopathies and patients with TLE including the ones with depressive-amnesic-psychotic syndrome and the role of RELN in gyrus dentate dispersion and cortical delaminating, and its possible effect on dynamic instability of microtubule (MT), we decided to analyze the evidence available about RELN/p-tau pathway dysfunction in patients with TLE because of FCD type IIIa and its possible role in the neuropsychiatric profile in this group of patients. This could not only help explaining the pathogenesis of TLE, but also to find new targets that could stop the ongoing process termed epileptogenesis in patients with perinatal insults that lead to TLE because of dysplasia type IIIa.

2. Methods

2.1. Search strategy

The current literature was reviewed using Cochrane, EMBASE, PROSPERO register, MEDLINE, and PubMed from 1995 to July 2018. The search was based on the following medical subject heading (MESH) and free text terms in the title and abstract: "reelin", "reelin and focal cortical dysplasia type IIIa", "reelin and cortical lamination", or "reelin and tau pathology", "tau phosphorylation" in combination with "temporal lobe epilepsy" both in animal models and humans with epilepsy and "hyperexcitability", "depressive symptoms", "psychosis", and "behavior changes".

2.2. Selection criteria and strategy

Articles of interest were reviewed by one investigator (RAM). If analysis of the title and abstract was insufficient to determine whether the article should be in- or excluded, the full text was reviewed.

The following articles were excluded: (1) if no mention was made about the histopathological features in TLE; (2) if insufficient information, to allow data of patients with different ages, to be distinguished; and (3) articles written in languages other than English and Spanish.

3. Results and discussion

3.1. TLE and cytoarchitectonic changes in temporal lobe cases of FCD type IIIa

Hippocampal sclerosis is characterized by neuronal cell loss in hippocampal subregions CA1, CA3, and CA4 accompanied by astrogliosis and loss of other interneurons as well as mossy cells in the hilus (CA4). Dentate gyrus granule cells are seldom affected by cell loss. However, their excitatory axons, the mossy fibers (MF), sprout backwards to the granule cell layer (GCL) [4]. Besides, granule cells are observed to show a dispersion of their normally dense and slim GCL, the cell loss is combined with mossy fiber sprouting (MFS). The 2013 International League Against Epilepsy (ILAE) classification of HS provides pathological identification of three distinct subtypes with a clinical predictive value based on the patterns of neuronal loss. Hippocampal sclerosis type 1 involves neuronal loss in the CA1, CA3, and CA4 regions, while HS type 2 involves CA1 neuronal loss only [11]. Hippocampal sclerosis type 3 describes neuronal loss restricted to CA4. Hippocampal specimens showing reactive gliosis with little/no neuronal loss are classified as 'no HS'. Hippocampal sclerosis subtype has shown clinical correlation with age of precipitating injury, early seizure onset, longer epilepsy duration prior to surgery, and also long-term seizure-free outcome posttemporal lobectomy [11].

Focal cortical dysplasia type IIIa, a cortical lamination abnormality associated with HS seen in some patients with refractory TLE, involves a number of histopathological features that in combination suggest that an abnormal tissue remodeling, where microtubule-associated proteins and protein related to migration in postnatal stages, may play an important role. In this variant, the temporal cortex shows alterations in the architectural organization (cortical dyslamination) or cytoarchitectural composition (hypertrophic neurons outside layer 5). Different variants have been described as follows: 1. - HS with architectural abnormalities in the temporal lobe, i.e., loss of layers 2 or 4. This category also includes the occurrence of hypertrophic neurons outside layer 5, which still share a pyramidal morphology and accumulate NF. HS with TLS; 2. - HS with TLS and heterotopic neurons in subcortical white matter; 3. - HS with TLS and small "lentiform" heterotopias in subcortical white matter; and 4. - HS with small "lentiform" heterotopias and heterotopias in subcortical white matter [4].

All of these pathologic changes mentioned above involve abnormal migration, mispositioning and polarity loss of neurons, and many changes in dendritic tree, positioning, direction, growth, and connectivity requiring obviously, changes in neuronal cytoskeleton.

3.2. Reelin and temporal lobe epilepsy

3.2.1. Dispersion of granular cells in sclerotic hippocampus and reelin

Normal granular cells layer in dentate gyrus can be seen in only 18.7% of patients suffering from TLE. Nevertheless, granular cells pathology occurs in more than 80% of the cases. About 37.5% of patients have a substantial granular cell loss (granular cell pathology type 1) but more than half of the patients have GCD, ectopic neurons or clusters of neurons in the molecular layer, or even bilamination (granular cell pathology type 2) [12].

Haas et al. studied by in situ hybridization the expression of RELN messeger ribonucleic acid (mRNAs) in a total of 22 temporal lobe tissue from patients who were undergoing anterior temporal lobectomy for medically intractable TLE. In this study, the authors reported an inverse correlation between the extent of GCD and RELN mRNA expression in individual cases with TLE [13]. This investigation showed a possible

link between RELN deficiency and an abnormal migration of dentate gyrus neurons in epileptic hippocampus [13].

In reeler mutant mice (mice lacking RELN), there is a severe alteration of hippocampal lamination. It has been assumed that RELN acts as a stop signal for migrating neurons [14]. A study using dentate gyrus neurons as a model of study in vivo and in vitro demonstrated that RELN exerts its effects, by acting on the radial glial scaffold required for neuronal migration. Migration defects of dentate granule cells, reminiscent of those seen in reeler mutants, have been shown in tissue from patients with TLE. Similar results have been reported by Frötscher et al. [15]. These findings showed that the RELN signaling pathway is essential for the correct positioning of human hippocampal neurons, and therefore, a RELN deficiency may be involved in the pathological changes associated with epilepsy.

There are many arguments favoring the hypothesis that RELN deficiency is related to migration of granular cells in dentate gyrus:

1. Paralleled to the development of GCD, a significant decrease in RELN mRNA synthesis is observed in the hippocampus underwent kindling [16].
2. Neutralization of RELN by application of the CR-50 antibody induced GCD [16].
3. Downstream RELN signaling molecules, such as disabled-1 (Dab1), have been found expressed in dentate granular cells progenitors [8,13].
4. Exogenous RELN increased detachment of chain-migrating neuroblasts in dentate gyrus, and a blockade of RELN signaling increased chain migration [8,13].

3.2.2. Reelin and focal cortical dysplasia IIIa in temporal lobe

During the development of the CNS, RELN controls the migration and laminar arrangement of neurons in various structures including the neocortex [1–9]. In the RELN-deficient mouse, the migration of neurons is severely altered in this region, resulting in a malformation of layers [17,18]. In the neocortex, RELN is synthesized and secreted by early-generated CR cells in the marginal zone underneath the pial surface [19]. The marginal zone is a cell-poor layer in wild-type mice, whereas in RELN-deficient mice, it is invaded by numerous neurons. Such finding suggests that RELN located at the surface of the cortex acts as a "stop" signal, terminating the migration of neurons from the ventricular zone to the cortical plate during development [20].

It has long been known that neurons from deep layers in the cerebral cortex are early-generated neurons, whereas later-generated neurons populate the more superficial layers [21]. In the reeler mutant, this inside–out lamination of the cortex is severely altered, and late-generated neurons fail to bypass their predecessors, resulting in an inversion of cortical layers [21].

It has been observed in early studies of the reeler mutants that many cortical pyramidal cells do not show the normal uniform orientation towards the pial surface, feature characteristic of wild-type animals, but instead are oriented in various directions, like neurons in FCD type Ia or Ib [22]. Apical dendrites of the neurons arise from the leading process of migrating neuroblasts. It is interesting to know that deficiency in RELN signaling leads to misorietation of the leading processes of migrating neurons, and that many of them do not reach the marginal zone [23]. In line to that Garbelli et al., observed CR cells were identified by using calretinin antiserum, in layer I of adult human temporal cortex from patients with epilepsy with architectural dysplasia (FCD type I), in comparison with normal cortex. The authors found a significant increase in the density of CR cells only in patients with architectural dysplasia. Whereas some of these CR cells were RELN immunoreactive, other does not. These findings suggest that differences in the persistence of CR cells or their functionability and development can be related to FCD type I [24].

The same idea was reported by Marucci et al., who described an immunohistochemically study of 30 cases of patients with FCD type IIIa. In the sample, there were 15 cases of abnormal cortical layering FCD type IIIa (8 cases without GCD and 7 cases with GCD type 1) and 15 cases of abnormal cortical layering associated with GCD type 2. In the first group, RELN-positive cells were observed in 53.3% of cases in the cortex and in the 86.6% in hippocampus. In contrast, in the second group, RELN-positive cells were observed in only 20% in the cortex and in 13.4% in the hippocampus. In cases where RELN activity was deficient, there was an increased motility of the dentate gyrus granule cells, which subsequently invaded the molecular layer, a condition designated as GCD type 2. Reelin cells are absent or extremely rare in cortical and hippocampal specimens when cases were characterized by abnormal cortical layering associated with HS and GCD type 2. These results might support the existence of a common pathogenetic link between RELN deficiency and FCD type IIIa with GCD type 2 [25]. To see how RELN can control migration of granular cells, neurons position, and dendritic orientation, see Fig. 1.

3.3. Tau and epilepsy

A growing body of evidence suggests that tau is involved in the pathogenesis of epilepsy. Diseases, such as AD, Parkinson's disease (PD), and Pick's disease, a well-known tau-positive neurodegenerative disorders, have seizures, whereas all tau-negative degenerative diseases, including frontal dementia of non-AD and non-Pick type diseases, are not associated with seizures. Patients with AD and other types of dementias have a greater risk of developing epilepsy compared with age-matched controls. In epilepsy, AD and PD have been reported similarities in terms of immunoreactivity for ubiquitin, amyloid b-protein, b-amyloid precursor protein (APP), apolipoprotein E (ApoE), and a-synuclein. These proteins have been found abnormally expressed both in animal models and in patients with epilepsy. Thus, epilepsy similar to AD may have an abnormal tau phosphorylation [28].

Sen et al. [29] were the first investigators to report a possible link between epileptogenesis, tau hyperphosphorylation, and neurodegeneration in a case–control study of patients with FCD, aged between three and a half months to six years, reporting that neurons within FCD areas showed tangles immunopositive for p-tau in all cortical laminae and also in heterotopic dysplastic neurons within the white matter. Besides, they reported a loss of cortical neurons in regions of FCD compared to the histological normal cortex in older children. The observed tau pathology resembled the AD tauopathy because of the immunoreactivity found, targets three-repeats (RD3) and four repeats (RD4) regions, the same phosphorylation demonstrated in patients with AD [29]. The fact that p-tau depended on the etiology of epilepsy, reinforced the idea of p-tau does not depend on seizure activity. The authors reported increased levels in tau phosphorylation in cerebrospinal fluid in patients with epilepsy of knowing etiology or patients with acute symptomatic seizures, different to patients with unknown etiology [30]. These results suggest that the increased of tau phosphorylation could be related to the etiology but not to the convulsion or seizure activity itself [30].

3.3.1. p-tau and mossy fiber sprouting in TLE

Mossy fiber sprouting have been documented in all pathologic studies of TLE. Mossy fiber sprouting is a well-known mechanism subjacent to epileptogenesis [31]. In 2010, Tian et al. studied a group of 240 male rats that developed behavioral kindled seizures and MFS in their hippocampus. The authors observed an overexpression of tau protein and its phosphorylation at Ser 202 over time [32]. The expression of p-tau showed a good correlation between the development of behavioral kindled seizures and the degree of MFS progression. This study implied definitively p-tau in MFS and in turn, in the epileptogenesis [33,34].

In the same line, Yan et al. observed that chronic recurrent epilepsy at a preplaque age has an accelerated amyloid beta (Ab) plaque pathogenesis, an increased intraneuronal p-tau expression, and neuronal loss in some temporal lobe regions. These results suggest that p-tau

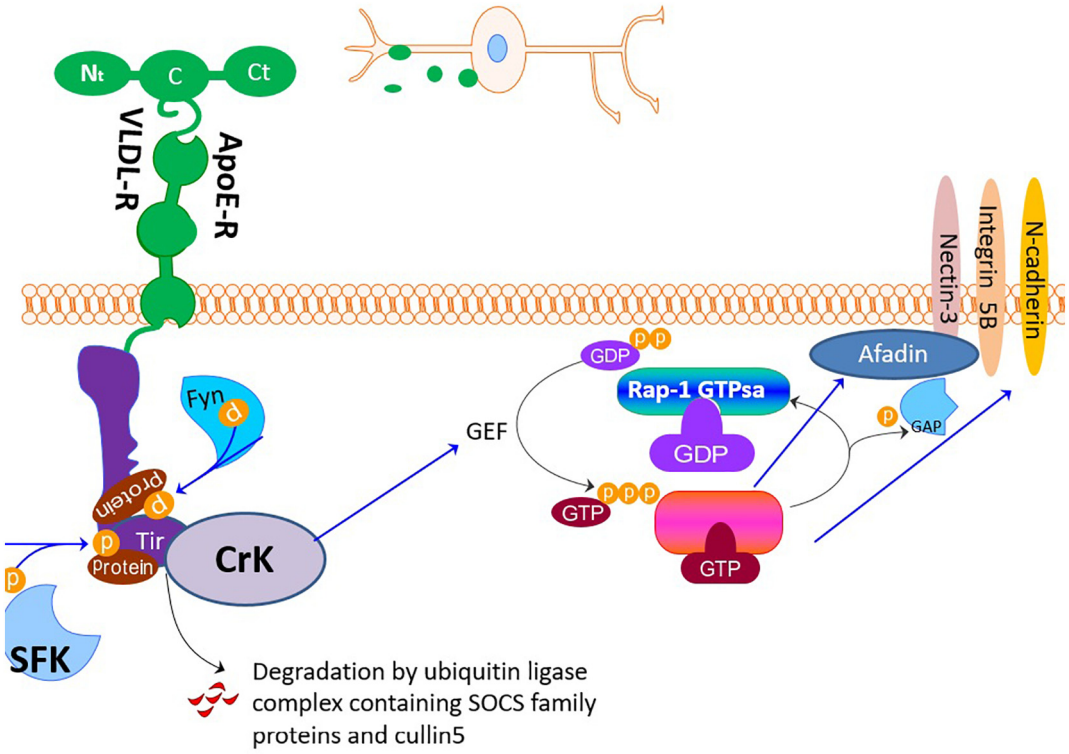

Fig. 1. Reelin signaling mechanism of neurons' migration, position, and synapses plasticity. Legend: Reelin signaling mechanism of neurons' migration, position, and synapses plasticity. Reelin is a protein with 3 domains, an Nt, a C, and a Ct domain. C domain binds lipoprotein receptors (ApoER2 and VLDLR). Its internalization is associated with Dab-1 phosphorylation by Src/Fyn kinases. Reelin controls granular cells' migration and cortical layer formation through the Crk/C3G/Rap1 pathway. Reelin exerts this function activating Rap-1 GTPsa which in turn activates adhesion molecules, including nectin3, N-Cadherin, and Integrin α5β1. Postnatally, the Crk adaptor proteins contribute to reelin activity by promoting protein translation, dendrite outgrowth, and spine development. Dab-1/SFK/Fyn/CrK complex is degraded by ubiquitin ligase complex containing SOCS family protein and cullin 5 [26,27].

overexpression could be potentially linked to aberrant synaptic/axonal plasticity in experimental epilepsy [35].

Additional evidence came from the study of Xi et al. using gene chips in specimens of brain from patients with pharmacoresistant focal epilepsy. The authors found an upregulation of genes associated with tau such as: MAP1A (microtubule-associated protein 1A), MAP2, P38, cell division protein kinase 5 (CDK5), myoglobin 1E (MYO1E), laminin beta 1 (LAMB1), tubulin gamma 1 (TUBG1), casein kinase 2 (alpha 1 polypeptide) (CSNK2A1), glycogen synthase kinase-3β (GSK-3β), and cadherin 18 type 2, LAMB1, CSNK2A1, and TUBD1 [36].

Human studies also support the notions of tau pathology in TLE. Tai et al., in a study of brain specimens taken from 33 patients with TLE, identified an unusual pattern of subpial tau deposition and colocalization with MFS. In this study, 57% of patients with TLE had rare or mild neuropil thread or occasional neurofibrillary tangle (NT). All patients in this group had HS and many MFS, an evidence of epilepsy-associated hippocampal network reorganization. Tau deposition spared the CA1 hippocampal subfields but in about 27.7% of the patients, tau deposition was found inside hippocampal regions and the subiculum resulted more affected. This is different to the features found in AD. In 11.1% of the cases showed reminiscent pattern of MFS. There was evidence of p-tau localized around neurofilament-positive neurons in CA4, supporting tau aggregation in the MF axons and terminals. Additional prominent staining was noted in the alveus, horizontal neurons in CA1, and axons in parahippocampal gyrus white matter. Also, they found a significant statistic association between tau deposition and the history of secondarily generalized seizures suggesting that tau deposition increases hyperexcitability or brain connectivity. In this study, the authors did not mention if FCD type Ia, Ib, or Ic were or not present in the neocortical temporal structures in this group of patients [5].

3.3.2. p-tau implies hyperexcitability

P-tau has been associated with hyperexcitability. In a well-designed study, Smart et al. used the Kcna1 −/− knockout mouse model of TLE and bang-sensitive Drosophila mutants, the author demonstrated the effect of p-tau in hyperexcitability. In these study, mutant mice lacking tau exhibited a 94% reduction in seizure frequency, 60% reduction in abnormal electrographic activity and in lethality. The protective effect on the premature lethality of tau lost was dose depending [37]. Thus, p-tau might play an important role in hyperexcitability, the hallmark of epilepsy and could explain, in part, the recurrent seizures.

This result was mirrored by Song et al. who performed additional experiments using bang-sensitive Drosophila mutants that exhibit increased propensity for behavioral seizures following mechanical stimulation. For the experiment, they used two different bang-sensitive Drosophila mutants: kcc that carries a mutation in a K+/Cl− cotransporter, and carrier of ethanolamine kinase (EAK) mutation. In both mutants, genetic reduction of tau resulted in a reduced hyperexcitability [38].

The above-described studies put p-tau as potential mechanism associated with hyperexcitability and seizure recurrence, well-known features of epilepsy, especially of TLE.

3.4. Tau pathology, memory, and neuropsychiatric complications in temporal lobe epilepsy

Mood disorders are the most frequent psychiatric comorbidity in patients with epilepsy. A study found a high frequency of lifetime psychiatric disorders (70%) in patients with TLE. The most frequent psychiatric complication is the presence of mood disorders (49.3%). Around 27.4% of the patients are depressed, and 9.6% met criteria for bipolar disorder. Anxiety disorders are also frequent (42.5%),

mainly generalized anxiety disorder (21.9%). Additionally, obsessive–compulsive disorder was present in 11.0% and psychotic disorders in 5.5% of patients [2].

Reelin has been associated with psychosis onset, depressive episodes, and changing mood, like in bipolar disorders in general population. Some evidence that supports the possible role of RELN and tau in psychiatric complications are as follows:

1. Corticosterone (CORT) causes a decreased in the number of RELN-immunopositive cells in the dentate gyrus subgranular zone (SGZ), where adult hippocampal neurogenesis takes place. The repetitive CORT injections produce depression-like symptoms in both rats and mice that are reversed by antidepressant treatment [39].
2. Downregulation of the number of RELN-positive cells runs parallel to the development of a depression-like symptoms during repeated CORT treatment [39].
3. Cotreatment of CORT and antidepressant drugs prevents both RELN deficits and the development of a depression-phenotype [39].
4. Reductions in RELN expression in hippocampus have been associated with schizophrenia, bipolar disorder, and major depression disorder [40]. Significant reductions of RELN positive cells were observed in the dentate molecular layer, CA4 area, and total hippocampal area of schizophrenics vs. controls [40].
5. Reelin-positive cell densities were also reduced in CA4 areas of subjects with bipolar disorder [40].
6. While stress increased NMDA NR2B-mediated synaptic transmission, known to be implicated in depression and anxiety, RELN overexpression significantly reduced it [41].
7. Interestingly, the molecular pathways subjacent to bipolar disorders were tested in a sample of ~7000 patients and controls. As a result, 3 out of the 18 tested pathways related to lithium action were found to be associated with bipolar disorder. The analysis showed that involved pathways were related to RELN. The obtained data point out to a possible involvement of RELN microtubule and related mechanics with affective disorders [42].
8. Reelin is 50% downregulated in postmortem psychotic brain of reeler mouse (+/RELN) [43].
9. Brain abnormalities in RELN deficiency are similar to psychotic brain and include a reduction in glutamic acid de carboxylase 67 (GAD67), dendritic arbors and spine density in cortex and hippocampus, and abnormalities in synaptic function including long-term potentiation (LTP) [43].
10. Reelin is hypermethylated in GABAergic neurons of psychotic postmortem brain and that DNA methyltransferase 1 (DNMT1) is upregulated. Hypermethylation of RELN in mice causes brain and behavioral abnormalities similar to those found in models of RELN deficiency [43].

Tau pathology has been also associated with psychosis onset, depressive episodes, and changing mood, like in bipolar disorders in general population. Some evidence that supports the possible role of RELN and tau in psychiatric complications are as follows:

1. The prefrontal cortex of 45 AD cases with psychosis had higher intraneuronal p-tau concentration than in subjects with AD without psychosis [44].
2. High cerebrospinal fluid (CSF) tau-protein concentration has been found in patients with delirium induced by high dose of psychiatric medication [45].
3. In a study of temporal lobe resection specimens from 47 patients with TLE was identified a distinctive MAP2 and tau deposition pattern around the hippocampal CA regions, and this result was correlated with cognitive and behavior complications.
   a) An increased tau expression in the CA2 region was associated with lower average of verbal scores.
   b) A decreasing tau expression in MTLE with psychosis.
   c) MAP2 and tau expression in the entorhinal cortex correlated inversely with granular layer dispersion [46].
4. Prada-Jardim et al. identified a subtle hyperphosphorylated tau within the dentate gyrus and subiculum which was significantly associated with naming score decline 1 year postoperatively [47].
5. Tai et al. examined 33 patients with TLE and found a significant correlation between the extent of tau pathology and decline in verbal learning, verbal recall, and graded naming test scores over 1-year postresection [5].

These evidence suggest a tau-related cognitive decline process in patients with TLE [5] and that neuropsychiatric complications in MTLE might rely on differential morphological and possibly neurochemical backgrounds.

3.4.1. Temporal lobe epilepsy shows a unique pattern of p-tau

Hyperphosphorylated tau pathology in the form of neuropil threads, NTs, and pretangles within temporal lobe tissue has been identified using immunohistochemistry for AT8 labeling (antibodies vs. tau phosphorylation at Ser202 or Thr 205 sites) in specimens obtained from humans suffering refractory TLE. The authors did not report whether the neocortical temporal cortex had or not associated with FCD. P-tau appears as a 'subpial' band of AT8 labeling with an axonal-like pattern. The deposition along the subpial region in temporal neocortex as a granular aggregates and the colocalization with MFS that spared hippocampal CA regions, constitutes a unique pattern of tau pathology [5]. Based on a double labeling with AT8 and RELN (CR cells marker) was demonstrated that the intense labeling with AT8 antibody does not overlap with the labeling of RELN. This might suggest that RELN deficiency is concomitant with abnormal tau phosphorylation [5]. These results were also confirmed in a separate study of 19 surgical specimens with TLE comparing p-tau distribution in this group of patients to brain specimens obtained from a small group of patients with posttraumatic encephalopathy [83].

Other atypical feature of the TLE tau pathology is the absence of Ab positive plaques in the majority of cases. In the study of Tai et al., Ab positive plaques were absent in 85% of patients with TLE [5]. A weak positive correlation was observed in this cohort between the modified tau score and age at time of surgery and age of epilepsy onset suggesting that p-tau could not be related to the time of epilepsy evolution what could, in turn, mean that p-tau could rely more on epileptogenesis than seizure recurrence itself [5].

3.5. How tau is phosphorylated and what is the evidence of this process in TLE?

Mossy fiber sprouting is observed in experimental models of TLE and in the epileptic human hippocampus. Previous studies have supported the hypothesis that MFS alters synaptic connectivity and circuit organization, thus forming recurrent excitatory connections, which contribute to an enhanced susceptibility to seizures [48]. In this review, we described that p-tau is implicated in MFS. Although different kinases may modify tau, it has been suggested that GSK-3β is important in regulating tau phosphorylation, including at Ser 202/Thr 205 residues, under physiological and pathological conditions [49].

Glycogen synthase kinase-3β is a constitutively active multifunctional serine/threonine kinase that is involved in regulating diverse physiological pathways, including neuronal structure, apoptosis, axon growth and guidance, cytoskeletal stability, and synaptic plasticity [50]. Previous studies have demonstrated that GSK-3β affects axoplasmic transport and axonal growth through the phosphorylation of tau protein [51]. It is thought that GSK-3β may also play an important role in epileptogenesis, particularly in MFS by a mechanism involving p-tau. In a study of human, TLE with HS was found a decreased in GSK-3β phosphorylated expression (a form of inactive enzyme). The

level of GSK-3β phosphorylated expression was inversely related to longer epilepsy history [52]. In the same line, Liu et al. found an increase of GSK-3β S9 and a decrease in GSK-3β Y216 in temporal lobe structures of patients with TLE that was interpreted as an overactivation of GSK-3β [53]. Although total p-tau was not significant statistically different, the radio p-tau/tau does. This result points to an excessive phosphorylation of tau in patients with TLE in whom GSK-3β is overfunctional.

Various studies have found that activation of GSK is associated with MFS. Huang et al. studied GSK-3β mRNA expression, GSK protein, and its activity in various regions of the hippocampus [34]. The authors found that the expression of GSK-3β mRNA and protein, as well as the GSK-3β activity, increased significantly with recurrent seizures over the weeks in epileptic mice. The GSK-3β activity was correlated with the progression of MFS in the CA3 area. The study concluded that GSK-3β might be involved in the progression of MFS and is important in epileptogenesis [34].

Similarly, Lee et al. demonstrated that the expression of GSK-3β was elevated after seizure induction, and the administration of lovastatin (which decreases the expression of GSK) significantly reduced the extent of MFS in both dentate gyrus and CA3 region in the hippocampus. The alteration of the expression level of GSK-3β after seizure induction suggests that GSK-3β can be associated with both MFS and epileptogenesis [54].

Although the possible relation among RELN, GSK-3beta activity, and p-tau have not been established in patients with TLE, data extracted from animal models support this hypothesis. Mice lacking RELN, double-knockouts lacking the very low density lipoprotein receptor (VLDLR) and ApoE receptor 2 (ApoER2), and mice lacking Dab1 display increased levels of p-tau. Paralleling the change in p-tau levels, a GSK-3beta activity increased in RELN-deficient mice has been observed [55]. In the next section, this complicate cascade of events will be described. Fig. 2 shows the RELN-tau phosphorylation pathway.

3.6. Putting everything together: the hypothesis of reelin-tau-p pathology

Reelin-deficient mice show a highly disorganized and delaminated cerebral cortex [57]. The final outcome is an increased in the excitability and a susceptibility to hippocampal and neocortical epileptiform activity [58]. In the absence of RELN, neuronal migration does not properly occur, and neocortical lamination is perturbed. This process can be explained throughout different mechanisms. Reelin might function as a chemo-attractant for migrating neurons, control the mechanism that initiates the inside–out lamination, and facilitate the detachment of neurons from radial glial processes and their subsequent differentiation [58,59]. A partial deficiency of RELN at some point of neurodevelopment can be related to cytoarchitectural abnormalities seen in FCD type IIIa (see Fig. 1 to understand the possible mechanism involved in cortical and dentate gyrus cytoarchitectural maintenance induced by RELN).

Reelin is also implicated in the dispersion of projection neurons observed in the stratum pyramidal and dentate GCL in reeler mice [60]. Granule cell dispersion is often observed in human MTLE; the dispersion is prevented or decreased with the infusion of RELN into hippocampal tissue. Besides, GCD correlates with hippocampal RELN loss in patients with MTLE [7]. Granule cell dispersion and loss of RELN were also observed in rodent models of MTLE [16,61]. It remains still to be elucidated whether RELN loss and GCD contribute to epileptogenesis, or if they are an effect of seizures [15].

The evidence of a dependency of tau phosphorylation on RELN deficiency is based on the following features: first;, the levels of site-specific tau phosphorylation increase in RELN-deficient mice as ApoE protein levels decrease (the highest levels of tau phosphorylation at Thr-172, Ser-387, and Ser-395 were seen in mice lacking RELN and ApoE (*RELN*$^{-/-}$ *ApoE*$^{-/-}$), followed by RELN $^{-/-}$*ApoE*$^{+/-}$ mice, and RELN$^{-/-}$ *ApoE*$^{+/+}$, whereas little immunostaining was observed in wild-type mice (RELN$^{+/+}$*ApoE*$^{+/+}$); second;, the levels of site-specific tau phosphorylation are increased in Dab1-deficient mice independent of ApoE protein; and third;, GSK-3β activity and protein levels are increased as ApoE protein levels decrease in RELN-deficient mice, but were independent of ApoE in Dab1-deficient mice. The concentration of immunoreactive GSK-3β was lowest in wild-type brain lysates and gradually increased in RELN-deficient, RELN-deficient and *ApoE*-reduced, and RELN- and *ApoE*-deficient lysates (Fig. 2 shows the RELN-tau phosphorylation pathway and how RELN deficit can be related to apoptosis) [55].

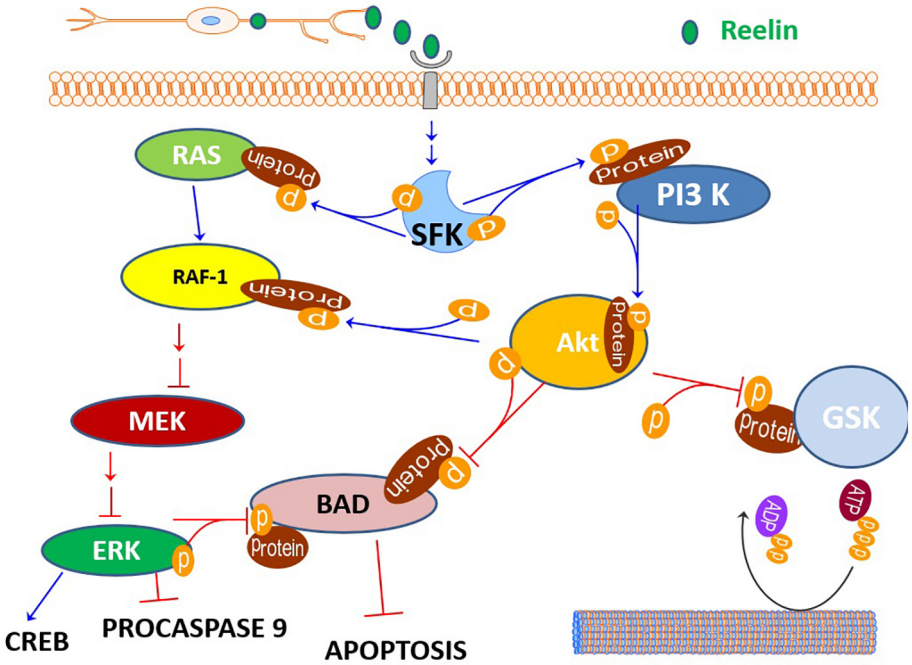

Fig. 2. Reelin/tau phosphorylation pathway and apoptosis. Legend: Through SFK/PI3K/Akt pathway activation, reelin inhibits GSK that prevent tau from phosphorylation. Also, BAD resulted inhibited from phosphorylation by AKt kinase and ERK. ERK remains active because RAF-1/MEK pathway is inhibited by Akt depending phosphorylation mechanism. Reelin affects synaptic function and plasticity in adult brain. An unknown receptor mediates the activation of the Erk1/2/CREB pathway by Akt kinases. This signaling pathway induces genes involved in synaptic plasticity and learning [56].

In case of RELN deficiency, the normal suppression of GSK-3β activity is not carried out, then, GSK-3β is activated which in turn would increase in tau phosphorylation. Tau phosphorylation lets MFS and hyperexcitability [62]. This model is based on several lines of evidence. First, RELN induces phosphorylation of Dab1, protein kinase B (PKB), and GSK-3β, an event that requires the presence of VLDLR and ApoER2 and binding of RELN to these receptors. Second, cells deficient in Dab1 are unable to induce phosphorylation of PKB or GSK-3β in response to RELN. Third, inhibitors of PI3K inhibit RELN-induced phosphorylation of PKB and GSK-3β but not of Dab1. Finally, several mediators of RELN signaling, including apoER2 and Dab1, are highly enriched in axonal growth cones [63]. Thus, these suggested that a RELN deficiency increased tau phosphorylation. Tau phosphorylation and the localization where it occurs seem to be specific for TLE [5,64] and are related to different psychiatric complications [5,46].

The sequence of signaling events initiated by RELN as proposed here is naturally linear. However, most signaling pathways are multifaceted, branching, and overlapping at various points. Thus, these commentaries do not exclude the role of other pathway and kinases.

4. Conclusion

Reelin deficit may determine an abnormal cortical lamination, apoptosis of hippocampal neurons, and dentate gyrus dispersion. Additionally, RELN deficiency might be associated with an abnormal tau phosphorylation. These processes can be associated with an abnormal hyperexcitability, neuropsychiatric complications, and a myriad of typical histopathological features seen in patient with TLE because of dysplasia type IIIa.

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Declarations of interest

None.

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