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Review

Role of LGI1 protein in synaptic transmission: From physiology to pathology

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ABSTRACT

Leucine-Rich Glioma Inactivated protein 1 (LGI1) is a secreted neuronal protein highly expressed in the central nervous system and high amount are found in the hippocampus. An alteration of its function has been described in few families of patients with autosomal dominant temporal lobe epilepsy (ADLTE) or with autoimmune limbic encephalitis (LE), both characterized by epileptic seizures. Studies have shown that LGI1 plays an essential role during development, but also in neuronal excitability through an action on voltage-gated potassium Kv1.1 channels, and in synaptic transmission by regulating the surface expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA-R). Over the last decade, a growing number of studies investigating LGI1 functions have been published. They aimed to improve the understanding of LGI1 function in the regulation of neuronal networks using different animal and cellular models. LGI1 appears to be a major actor of synaptic regulation by modulating trans-synaptically pre- and post-synaptic proteins. In this review, we will focus on LGI1 binding partners, "A Disintegrin And Metalloprotease (ADAM) 22 and 23", the complex they form at the synapse, and will discuss the effects of LGI1 on neuronal excitability and synaptic transmission in physiological and pathological conditions. Finally, we will highlight new insights regarding N-terminal Leucine-Rich Repeat (LRR) domain and C-terminal Epitempin repeat (EPTP) domain and their potentially distinct role in LGI1 function.

1. Introduction

Leucine-Rich Glioma Inactivated Protein 1 (LGI1) is a 60-kDa protein, highly expressed in the central nervous system (CNS), that exhibits a strong expression profile in the hippocampus (Senechal et al., 2005). LGI1 interacts with proteins of the "A Disintegrin And Metalloprotease (ADAM)" family such as ADAM22 and ADAM23 (Ohkawa et al., 2013; Sagane et al., 2008). LGI1 is secreted by neurons and is composed of an N-terminal domain enriched in Leucine, called Leucine-Rich Repeat domain (LRR), and a C-terminal Epitempin (EPTP) repeat domain (Fig. 1.a). Mutations of the *LGI1* gene have been found in patients with a rare inherited form of epilepsy called autosomal dominant temporal lobe epilepsy (ADLTE) (Kalachikov et al., 2002; Morante-Redolat, 2002). Investigations on how dysfunctions of LGI1 cause epileptic seizures attributed an essential role of LGI1 during the maturation of the neuronal network in the CNS (Zhou et al., 2009). More recently, auto-antibodies (Abs) against LGI1 have been described in a subtype of adult patients with autoimmune limbic encephalitis (LE) (Irani et al., 2010;

Abbreviations: LGI1, Leucine-Rich Glioma Inactivated Protein 1; ADLTE, Autosomal dominant temporal lobe epilepsy; AMPA-R, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; ADAM, A Disintegrin And Metalloprotease; LRR, Leucine-Rich Repeat domain; EPTP, Epitempin domain; (m)Abs, (monoclonal) Auto-antibodies; (LGI1-)LE, (LGI1) limbic encephalitis; CNS, central nervous system; KO, knock-out; NMDA-R, *N*-methyl-D-aspartate receptors; FBDS, Facio-brachial dystonic seizures; HLA, Human leukocyte antigen; REM, Rapid eye movement; FLAIR, Temporal fluid-attenuated inversion recovery; EEG, Electroencephalogram; SLADH, Syndrome of inappropriate secretion of antidiuretic hormone; ADPEAF, Autosomal dominant partial epilepsy with auditory features; TARP, Transmembrane AMPA-R regulatory protein; mEPSC, Miniature excitatory post-synaptic currents; CSF, cerebrospinal fluid.

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Lai et al., 2010). LE with LGI1-Abs (LGI1-LE) is one of the most common type of LE and the Abs seem to play a direct role in the memory deficits and epileptic seizures characteristic of this disease (Ohkawa et al., 2013; Petit-Pedrol et al., 2018; Hébert et al., 2020). Thereby, studying and understanding the pathologies associated with LGI1 disturbance, are essential to improve diagnosis and treatment for these diseases. For this, it is necessary to investigate the underlying mechanisms regulated by LGI1 and to understand the processes by which LGI1 mutations or Abs disturb these mechanisms.

Thus, to better understand how dysfunctions of LGI1 caused by mutations or Abs lead to epileptic seizures and cognitive disorders, cellular and murine models targeting LGI1 have been developed.

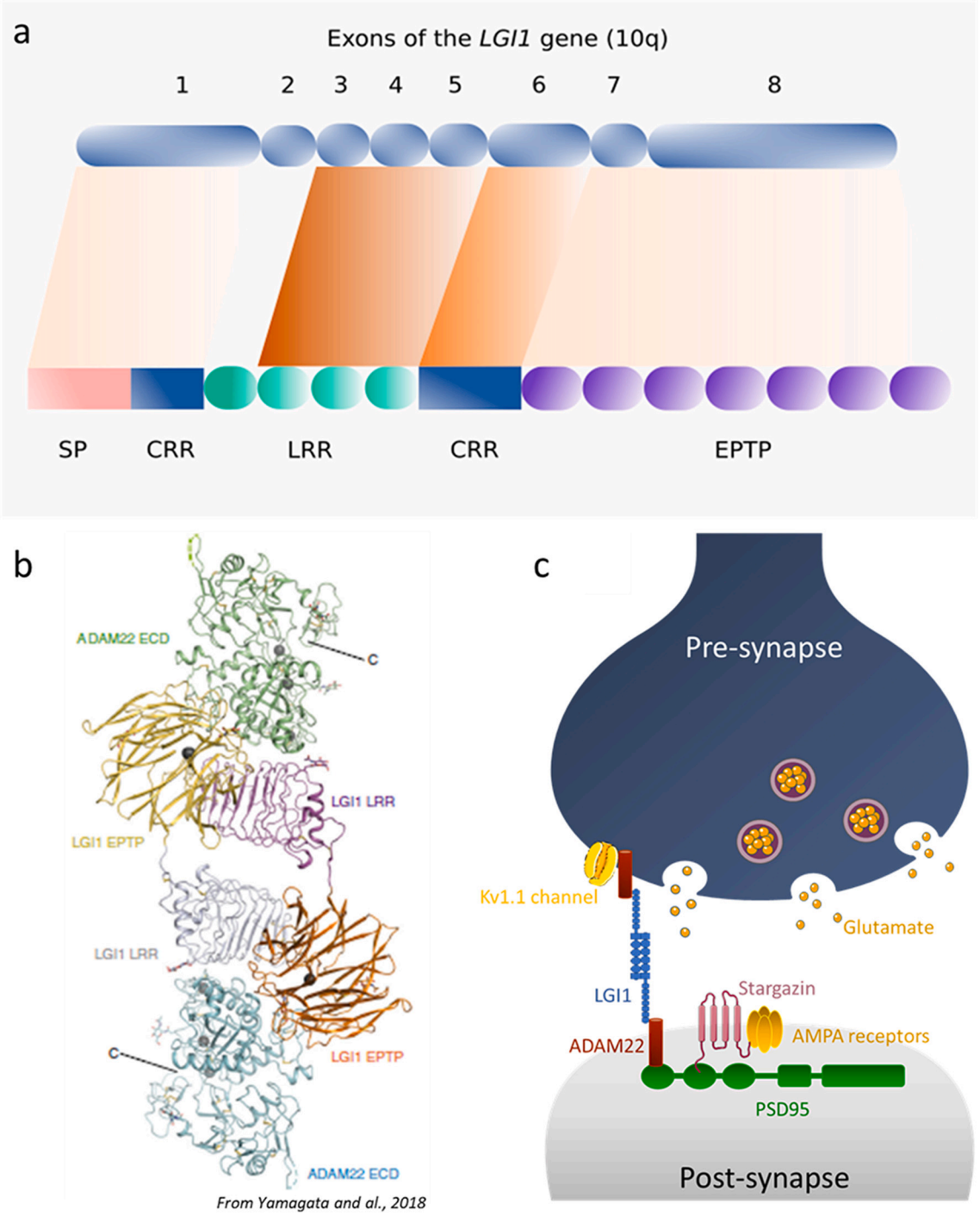

Fig. 1. *LGI1* gene structure and interaction. The *LGI1* gene is located on chromosome 10q and is composed of exon 1, encoding the signal peptide (SP) and the first cysteine-rich region (CRR), exons 2–5, encoding the LRR domain, exon 6, encoding the second CRR, and exons 7–8, encoding the EPTP domain. In LGI1 encephalitis patients, mutations occur throughout the *LGI1* gene, but the density of mutations (illustrated here according to the intensity of the orange polygons) is particularly elevated in exon 4 and also in exons 3 and 5 (a). The LGI1-ADAM22 complex interaction. The LRR domain of a first LGI1 protein interacts with the EPTP domain of a second LGI1 protein to form a homodimeric complex. The EPTP domain of LGI1 interacts with the ADAM22 protein. From Yamagata et al. (2018). (b) The LGI1-ADAM22 complex forms a trans-synaptic complex connecting pre- and post-synaptic proteins. The post-synaptic ADAM22 interacts with the PDZ-domain of PSD95 and modulates AMPA-R through the regulatory protein Stargazin, which also binds to PSD95. At the pre-synaptic side, LGI1 binds ADAM22 or ADAM23 and modulates Kv1.1 channel (c).

Notably, mice knocked-out (KO) for *Lgi1* have been engineered, and they exhibit epileptic seizures at 2 weeks of age leading to death at about 3 weeks of age (Fukata et al., 2010). Later on, a model of mice infused with LGI1-Abs has allowed improving the understanding of LGI1 synaptic function (Petit-Pedrol et al., 2018). LGI1 has an essential role during the maturation of the neuronal network by acting on the refinement of the dendritic tree (Zhou et al., 2009), but it is also important in the regulation of synaptic transmission in the mature neuronal network (Petit-Pedrol et al., 2018). LGI1 regulates the neuronal network at different stage of life by modulating neuronal excitability through Kv1.1 potassium channel expression (Petit-Pedrol et al., 2018; Schulte et al., 2006; Seagar et al., 2017) and by acting on the expression of AMPA-R (Fukata, 2006; Fukata et al., 2010; Lovero et al., 2015; Ohkawa et al., 2013; Petit-Pedrol et al., 2018). LGI1 is involved in all these mechanisms through its interaction with its transmembrane partners ADAM22 and ADAM23.

Herein, we reviewed the CNS diseases related to LGI1 alterations (Table 1) and the consequences on synaptic transmission and neuronal excitability.

2. Diseases related to LGI1

2.1. Familial LGI1 mutations: Clinical characteristics

ADLTE, also known as autosomal dominant partial epilepsy with auditory features (ADPEAF), is an uncommon genetic focal epilepsy syndrome (Ottman et al., 1995; Poza et al., n.d.). There is no sex predominance, and the first manifestations occur usually at the age of 18 years old, although the onset may vary from the early childhood to the fifth decade of life (Table 1). Clinically, ADTLE is characterized by focal seizures originating from the lateral temporal lobe, generally concomitant with auditory symptoms that may appear before the seizures as an aura or during a seizure as part of the ictal phase; receptive aphasia may also be either part of the aura or an ictal manifestation (Brodtkorb et al., 2002; Michelucci et al., 2003; Winawer et al., 2000). Additionally, patients may often have sensory, autonomic, and emotional symptoms, while secondary generalized seizures appear in more than 90% of the cases (Brodtkorb et al., 2002; Michelucci et al., 2003; Winawer et al., 2000). No neuroimaging abnormalities have been reported and interictal electroencephalograms (EEG) are often normal. Patients usually respond well to antiepileptic drugs, achieving complete seizure-freedom at least for generalized seizures, although nearly half of them continue to present focal seizures (Table 1) (Winawer et al., 2000; Brodtkorb et al., 2002; Michelucci et al., 2003).

Table 1
Comparison of the main characteristics of ADTLE and LGI1-antibody encephalitis. Abbreviations: ADTLE, autosomal dominant temporal lobe epilepsy; CSF, cerebrospinal fluid; EEG, electroencephalogram; FBDS, faciobrachial dystonic seizures; HLA, human leukocyte antigen; LGI1, leucine-rich glioma-inactivated 1; MRI, magnetic resonance imaging.

	ADLTE	LGI1-antibody encephalitis
Age at onset	18 years	65 years
Sex predominance	No	Men ≈65%
Pathophysiology	Genetic 30% mutations in LGI1 20% mutations in RELN or MICAL1 50% unknown	Autoimmune Autoantibodies against LGI1 Genetic predisposition ≈90% HLA-DRB1*07:01
Seizures	Lateral temporal lobe seizures (>95%), typically with auditory symptoms Generalized tonic-clonic seizures (>90%)	Medial temporal lobe focal seizures (70–90%), typically with piloerection & bradycardia Generalized tonic-clonic seizures (≈50%) Faciobrachial dystonic seizures (pathognomonic, ≈50%)
EEG abnormalities	Interictal temporal abnormalities (≈50%)	Interictal temporal abnormalities (≈30%) Contralateral slow wave & electrodecremental response (FBDS)
Other clinical features	–	Cognitive deficits (>90%) Psychiatric symptoms (60–90%) Sleep disturbances (≈40%) Hyponatremia (≈60%)
MRI	Normal	Limbic hyperintensities (≈60%)
CSF	–	Inflammatory abnormalities (≈50%)
Treatment	Antiepileptic drugs	Immunotherapy
Prognosis	Seizure-freedom ≈50% for focal seizures, ≈100% for generalized seizures	Seizure-freedom (≈90%) Cognitive deficits (60–75%)

Approximately 30% of families with ADLTE have mutations in the *LGI1* gene located on chromosome 10q (Fig. 1.a). The remaining patients have mutations in other loci, such as *RELN* (7q) and *MICAL1* (6q) genes, although the genetic basis is still unknown in up to 50% of cases (Dazzo et al., 2018; Michelucci et al., 2017). *RELN* mutations seem to provoke a deficit in reelin secretion; this protein regulates cytoskeleton remodeling during neural development, being also involved in dendritic growth and synaptic plasticity (Michelucci et al., 2017). Similarly, *MICAL1* mutations cause an increased activity of the MICAL1 protein, altering the assembly of the actin filaments in the neural cytoskeleton (Dazzo et al., 2018). Nevertheless, whether an interaction between these two proteins or with LGI1 exist, is still unknown. However, there is not a clear correlation between genotype and phenotype, and patients with distinct mutations are clinically indistinguishable (Dazzo et al., 2018; Michelucci et al., 2017). Every LGI1 mutation is usually present in one single family, and the average penetrance has been reported to be nearly 70%; *de novo* mutations are extremely rare (Rosanoff and Ottman, 2008). Mutations have been described to occur across the entire *LGI1* gene sequence, but their density is especially high in the exons 3–5 encoding the LRR domain (Fig. 2.a) (Ho et al., 2012). More than 40 mutations have been reported so far, nearly two thirds are missense mutations and one third corresponds to truncation and deletion mutations (Ho et al., 2012; Yamagata and Fukai, 2020). Most pathogenic mutations lead to a deficient LGI1 secretion, likely due to a misfolding of the truncated protein, while other mutations without associated secretion impairment seem to decrease the affinity of LGI1 for its partners ADAM22 and ADAM23 (Sirerol-Piquer et al., 2006; Yokoi et al., 2015; Dazzo et al., 2018; Yamagata and Fukai, 2020).

As *LGI1* genetic mutations lead to epilepsy in patients, this protein plays probably an essential role in neuronal network regulation. Thereby, investigating the mode of action of LGI1 is crucial to understand the mechanism underlying neuronal transmission, but also to provide adapted treatments to patients suffering from ADLTE.

2.2. LGI1 limbic encephalitis

LGI1-LE represents the second most frequent type of antibody-mediated autoimmune encephalitis after *N*-methyl-D-aspartate receptor (NMDAR)-Abs encephalitis (Hébert et al., 2020). In contrast to NMDAR-Abs and other types of autoimmune encephalitis that typically present a subacute onset, LGI1-LE displays a more protracted and sometimes subtle presentation (Irani et al., 2010; Lai et al., 2010). Furthermore, the demographic profile of LGI1-Abs encephalitis patients highly differs from the one of NMDAR-Abs encephalitis patients, since the latter are typically 65-year-old (on average) men (Ariño et al., 2016; Irani et al., 2010; Lai et al., 2010; Muñiz-Castrillo et al., 2021; van Sonderen et al., 2016). In addition, the clinical picture of LGI1-LE displays prominent involvement of limbic areas on the one hand with cognitive impairment and temporal lobe seizures, and motor cortical areas on the other hand with facio-brachial dystonic seizures (FBDS) (Navarro et al., 2016). Although the clinical phenotype of LGI1-LE is now well characterized, the pathogenic mechanisms that lead to the immune tolerance breakdown against LGI1 are still unknown. Indeed,

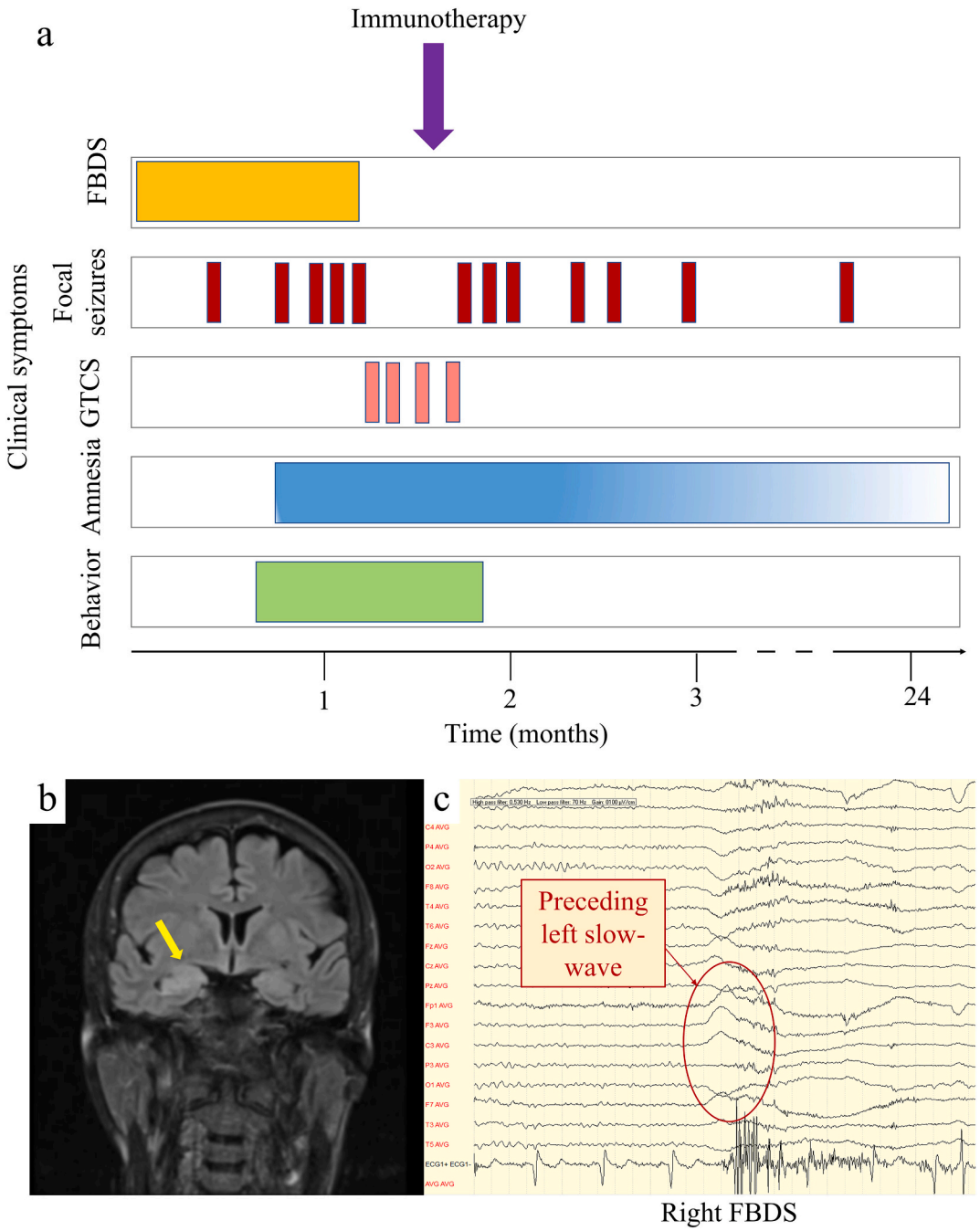

Fig. 2. Clinical vignette of a patient with LGI1-Abs encephalitis. A 53-year-old woman with autoimmune thyroiditis developed frequent, stereotypical, jerky movements involving her right arm and leg. One month later, the patient developed temporal lobe seizures along with behavioral changes and prominent anterograde memory dysfunction (a). After hospital admission, a brain MRI showed FLAIR hyperintensity involving the mesial temporal lobes (R > L) (b). Video-EEG analysis permitted to characterize the abnormal movements as FBDS that were consistently preceded by a contralateral frontal slow wave (c). Immunotherapy with intravenous corticosteroids and immunoglobulin was administered with marked clinical improvement but persistence of mild memory disturbances at last follow-up (2 years after onset).
Abbreviations: FLAIR: fluid-attenuated inversion recovery; MRI: magnetic resonance imaging; FBDS: faciobrachial dystonic seizures; GTCS: generalized tonic-clonic seizures; Video-EEG: video-electroencephalogram.

no infectious trigger has been reported so far, and tumor associations are extremely uncommon (10%) and controversial (van Sonderen et al., 2016). However, a strong association with human leukocyte antigen (HLA) DRB1*07:01, which is carried by nearly 90% of patients, has been recently described (Binks et al., 2018; Kim et al., 2017; van Sonderen et al., 2017; Mueller et al., 2018; Muñiz-Castrillo et al., 2021), suggesting that genetic predisposition and altered LGI1-derived peptides presentation might be important in the pathogenesis of the disease (Table 1) (Binks et al., 2018; Kim et al., 2017).

FBDS are considered as pathognomonic of LGI1-LE, being a very strong clue towards this diagnosis when present (nearly half of the patients) (Irani et al., 2011, 2010; Vogrig et al., 2020). Their anatomical origin is unclear, although it seems to involve both the motor cortex and the basal ganglia based on data from magnetic resonance imaging (MRI) and positron emission tomography (PET) studies (Boesebeck et al., 2013; Flanagan et al., 2015; Navarro et al., 2016). They consist in very

brief contractions of the upper limb, often involving also the ipsilateral hemiface, and more uncommonly the lower limb, which may lead to falls. They are usually unilateral at onset but generally become bilateral later in the course of the disease, alternating from side to side (Vogrig et al., 2019). FBDS can repeat very frequently, up to several hundred episodes per day. They may appear even during sleep, and might be triggered by emotions or position changes (Irani et al., 2011). Typically, FBDS appear first, and are later followed gradually by temporal lobe focal seizures, then cognitive dysfunction, and finally tonic-clonic seizures (Fig. 2.a) (Irani et al., 2011; van Sonderen et al., 2016). Cognitive impairment is usually severe and comprises both amnesic and executive functions (Ariño et al., 2016; Finke et al., 2017). In addition, apathy is frequent but patients may also show impulsive behavior, and even aggressiveness against themselves or their relatives (Ariño et al., 2016; Finke et al., 2017). Sleep disturbances are common, such as insomnia and rapid eye movement (REM) sleep behavior disorder, as well as dysautonomia, mainly hyperhidrosis (Ariño et al., 2016; Irani et al., 2010; van Sonderen et al., 2016).

Diagnosis of LGI1-LE may be challenging due to its progressive course that might be confounded with neurodegenerative disorders. Moreover, temporal fluid-attenuated inversion recovery (FLAIR) hyperintensities do not constitute a constant finding as they appear in approximately two thirds of patients (Fig. 2.b), while inflammatory CSF abnormalities are observed in only 50% (Ariño et al., 2016; Irani et al., 2010; van Sonderen et al., 2016; Muñiz-Castrillo et al., 2021). Similarly, at the early stages of the disease, EEG recordings can be normal even during FBDS, also hindering or delaying an accurate diagnosis. Even in cases of reportedly normal or nonspecific EEG alterations, a re-evaluation can reveal subtle but distinctive alterations prior to FBDS, usually in the form of a slow-wave contralateral to the FBDS (Fig. 2.c), or an ictal flattening of the EEG signal (electrodecremental response) (Navarro et al., 2016; Steriade et al., 2016; Vogrig et al., 2019). Hyponatremia due to a syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has been described as a typical finding, but is only present in 15–25% of patients (Ariño et al., 2016; Irani et al., 2010; Muñiz-Castrillo et al., 2021; van Sonderen et al., 2016). Regarding LGI1-Abs, it is noteworthy that in contrast to other types of autoimmune encephalitides, the detection seems to be more sensitive in the serum than in the CSF (Gadoth et al., 2017; Muñiz-Castrillo et al., 2020; van Sonderen et al., 2016); it is therefore of major importance to test both types of samples when there is a clinical suspicion of LGI1-LE (Muñiz-Castrillo et al., 2021).

Immunotherapy is considered effective in LGI1-LE, especially when administered early in the course of the disease (Fig. 3) (Irani et al., 2010; Lai et al., 2010; van Sonderen et al., 2016). Steroids have been shown to prevent cognitive disturbances in patients presenting only with FBDS (Irani et al., 2013, 2011), with cessation rates of nearly 50% and 90% after 30 and 90 days of treatment, respectively (Thompson et al., 2018). Moreover, it was shown in the study that FBDS was achieved earlier with prompt immunotherapy in the absence of cognitive impairment (Thompson et al., 2018). Steroids were also the most frequently drugs used as first line immunotherapy in other large cohort, with initial response rates higher than 95%, although nearly 75% of the patients required maintenance immunosuppression (Gadoth et al., 2017). Intravenous immunoglobulin has been widely used as first line immunotherapy as well, alone or in combination with steroids (Ariño et al.,

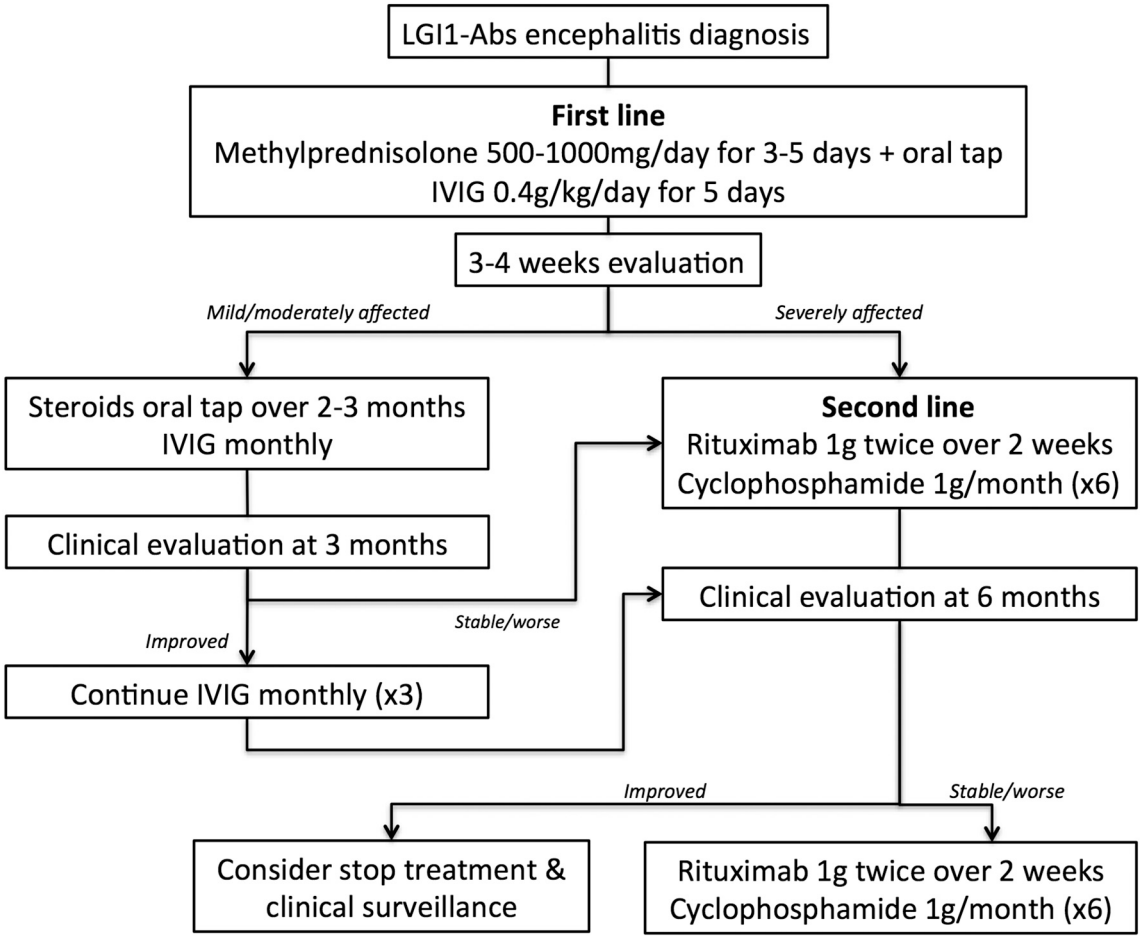

Fig. 3. Proposed therapeutic algorithm for LGI1-Abs encephalitis.
Abbreviations: Abs, antibodies; IVIG, intravenous immunoglobulin; LGI1, leucine-rich glioma-inactivated 1.

2016; Muñiz-Castrillo et al., 2020; Thompson et al., 2018; van Sonderen et al., 2016). Recently, they have been shown to have a positive effect in seizure control in a small clinical trial (Dubey et al., 2020). Rituximab and cyclophosphamide are often used as second-line treatment in up to half of patients, although they have not been associated with better outcomes, likely due to the fact that they are more commonly used in severely affected patients (Ariño et al., 2016; Finke et al., 2017; Muñiz-Castrillo et al., 2020; Sola-Valls et al., 2020). However, up to 75% of patients present some degree of long-term cognitive impairment despite (Fig. 2.a) (Ariño et al., 2016; Muñiz-Castrillo et al., 2020; Sola-Valls et al., 2020; van Sonderen et al., 2016), reflecting that current management must be improved. Main cognitive sequelae include disturbances of verbal memory, fluency, and visuospatial abilities, very often accompanied by depression, anxiety, and fatigue in more than 50% of the patients (Binks et al., 2021; Sola-Valls et al., 2020). Conversely, long-term epilepsy is uncommon, being reported in nearly 10% of the cases (Table 1) (de Bruijn et al., 2019; Muñiz-Castrillo et al., 2021).

One of the remaining questions is to understand why these LGI1-Abs are present in the serum and the CSF and what are their origins. Recent results are in favor of an intrathecal synthesis of monoclonal Abs (mAbs) in the CSF due to a chronic exposition to the antigen (Kornau et al., 2020; Lehmann-Horn et al., 2020). This result raised two questions to tackle: the first is to determine how LGI1-Abs are produced at the periphery, and the second is to understand how B cells secreting LGI1-Abs passed the blood-brain barrier to reach the CSF. Moreover, recent studies have highlighted that LGI1-Abs are polyclonal and are able to react against both EPTP and LRR domains at the same ratio in the serum and, most of the time, in the CSF (Ramberger et al., 2020). Interestingly, these studies assumed both mAbs are pathogenic whereas until then, only the EPTP reactive mAbs were assumed to be pathogenic (Kornau et al., 2020; Ohkawa et al., 2013; Ramberger et al., 2020).

3. The LGI1 synaptic complex

LGI1 protein is highly expressed in the CNS and particularly in the hippocampus. LGI1 is composed of an N-terminal LRR domain that is involved in LGI1 homodimerization through the residue E123. This residue interacts with the residue R474 of the C-terminal EPTP domain (Yamagata and Fukai, 2020). Thus, the C-terminal EPTP domain is essential for the homodimerization of LGI1 but also for its interaction with its transmembrane partners belonging to the ADAMs family members: ADAM22 and 23 (Ohkawa et al., 2013; Yamagata et al., 2018; Yamagata and Fukai, 2020) (Fig. 1.b). Although the ability of LGI1 to bind ADAM23 has been shown using ELISA tests (Sagane et al., 2008), or transfected HEK cells (Petit-Pedrol et al., 2018), the direct interaction in physiological conditions remains to be proven.

ADAM22 belongs to the PSD95 complex, found at excitatory synapses, and is anchored to PSD95 through its PDZ domain (Han and Kim, 2008; Hsia et al., 2019). It has been demonstrated that LGI1 indirectly regulates AMPA-R surface expression thanks to PSD95 interaction with Stargazin (Fukata, 2006). Stargazin is a transmembrane AMPA-R regulatory protein (TARP) that has been co-immunoprecipitated with LGI1 and ADAM22 (Fukata, 2006). Recently, it has been shown that LGI1-ADAM22 complex forms a trans-synaptic heterodimer complex (Fig. 1.c) (Fukata et al., 2021; Yamagata et al., 2018). Indeed, LGI1-ADAM22 pre-synaptic complex interacts with LGI1-ADAM22 post-synaptic complex. This trans-synaptic complex is essential for the nano-alignment of pre-synaptic proteins with post-synaptic proteins, which is fundamental for efficient synaptic transmission (Fukata et al., 2021). Thus, the LGI1-ADAM22 complex is at the center of a large protein complex including various pre- and post-synaptic proteins essential for proper synaptic organization (Fukata et al., 2021).

4. LGI1 function in the CNS

4.1. Developmental troubles

In order to understand the function of LGI1 in the regulation of the neuronal network and to investigate the causal link between LGI1 mutations and epileptic seizures, mouse models KO for the *Lgi1* gene have been generated (Boillot et al., 2016; Fukata et al., 2010; Zhou et al., 2009). These mouse models developed an epileptic seizure phenotype directly linking the genetic alteration of *LGI1* to epilepsy (Fukata, 2006). Only homozygous mice triggered severe epileptic seizures whereas heterozygous mice did not, even if they presented increased susceptibility to epileptogenic drugs (Fukata et al., 2010). The lack of LGI1 is concomitant with developmental troubles that are lethal for the animal (Zhou et al., 2009; Fukata et al., 2010). Indeed, *Lgi1* KO mice display epileptic seizures from 2 weeks after birth and die by 3 weeks after birth (Fukata et al., 2010). In other studies, mice expressing a truncated form of LGI1 found in patients with ADLTE were developed to investigate the specific mutations found in this disease (Yokoi et al., 2015; Zhou et al., 2009). In these transgenic lines, LGI1 alteration was either due to a defective secretion or to an inability to bind to its partner ADAM22 (Yokoi et al., 2015). These ADLTE mutations led to epileptic seizures and death 3 weeks after birth, as observed for the LGI1-KO mice (Yokoi et al., 2015). Mice mutated in the EPTP domain of LGI1 displayed neuronal network development defects with an increased synaptic density due to an impairment in dendritic refinement (Zhou et al., 2009). Indeed, during the maturation of the neuronal network, the very developed dendritic tree is pruned, and some dendritic spines are removed (Rihn and Claiborne, 1990). Because of the epileptic seizures triggered by a dysfunction of LGI1 protein, electrophysiological recordings were performed to investigate the glutamatergic transmission in transgenic mice mutated for *Lgi1*. Studies showed that loss of LGI1 increased excitatory synaptic transmission whereas an overexpression of LGI1 decreased glutamatergic synaptic transmission (Boillot et al., 2016; Fukata, 2006; Zhou et al., 2009). Further studies investigated the molecular cause for this increase in glutamatergic transmission and revealed that the loss of LGI1 decreased ADAM22 overall expression (Fukata et al., 2010; Yokoi et al., 2015) but also modulated Kv1.1 channels and AMPA-R expression (Lovero et al., 2015; Zhou et al., 2009).

4.2. Neuronal excitability through kv1.1 channels

Kv1.1 channels belong to the *Shaker* family of Kv channels. Kv1.1 are highly expressed in the hippocampus where they are co-expressed with other channels of the *Shaker* family, comprising Kv1.4 channel and Kvβ1subunit (D'Adamo et al., 2020). Kv1.1 are low-voltage activated channels that are rapidly inactivated when there are co-expressed with Kv1.4 and Kvβ1 (D'Adamo et al., 2020; Dodson and Forsythe, 2004). Kv1.1 is part of the large complex of protein formed by LGI1-ADAM22 trans-synaptic complex (Fukata et al., 2021). A first study investigated the regulation of kv channels belonging to the voltage gated potassium channels complex (VGKC) by the LGI1 protein (Schulte et al., 2006). They transfected oocytes with plasmid expressing kv1.1, kv1.4, and kvβ1 channels and recorded by electrophysiology the potassium current when they added endogenous LGI1. They observed that LGI1 prevents the rapid inactivation of Kv1.1 channels through Kvβ1 subunits (Schulte et al., 2006). Thereby, LGI1 may modulate Kv1.1 channel opening kinetics or surface expression (Schulte et al., 2006; Fukata et al., 2010). It is noteworthy that in the latter study, LGI1 function has been investigating on transfected oocytes that did not express ADAM22 (Schulte et al., 2006). Nevertheless, the role of LGI1-ADAM22 on Kv1.1 channels has been confirmed in another study, investigating the effect of ADAM22 or ADAM23 and LGI1 on kv1.1 current (Lancaster et al., 2019). They showed that in HEK Ad293 cells co-transfected with ADAM22 and Kv1.1 channels, ADAM22 alone had no effect on Kv1.1 currents, while the presence of LGI1 with ADAM22 increased Kv1.1 currents (Lancaster

et al., 2019).

Ex vivo studies investigated the underlying mechanisms of epileptic seizures in transgenic mice for *Lgi1*. Using early post-natal KO mice they have recorded an epileptiform activity due to an increase in glutamatergic synaptic transmission on CA1 region of hippocampal slices (Boillot et al., 2016). Regarding the absence of effect on the post-synaptic compartment, the authors suggested that the epileptic activity was caused by an alteration of the presynaptic compartment. Taking into account the presynaptic localization of Kv1.1 channels (D'Adamo et al., 2020; Dodson and Forsythe, 2004), this result also supports the idea of a modulation of Kv1.1 channels by LGI1.

Altogether, these studies show that LGI1 modulates Kv1.1 channels. However, mechanisms underlying the regulation of kv1.1 expression by LGI1 are still unknown. Thus, future studies should determine if LGI1 regulates kv1.1 through ADAM22 or ADAM23, and if there are other intermediate proteins recruited in this regulation. Then, it will be important to investigate the mode of action of this regulation to know whether LGI1 directly or indirectly regulate the surface expression of kv1.1 channels. The neuronal network development abnormalities observed in transgenic mice (Fukata et al., 2010; Zhou et al., 2009) makes difficult the specific investigation of Kv1.1 channel functions in a mature neuronal network. Thus, further studies are needed to clearly decipher the mechanism of LGI1 modulation on Kv1.1 channel function.

4.3. Synaptic transmission through AMPA receptors

AMPA-R are excitatory post-synaptic receptors involved in glutamatergic synaptic transmission (Sheng and Lee, 2001). AMPA-R are regulated by LGI1-ADAM22 complex (Fukata, 2006; Lovero et al., 2015; Ohkawa et al., 2013). Indeed, ADAM22, the transmembrane partner of LGI1, interacts with PSD95, the scaffolding protein of excitatory synapses (Fukata, 2006). PSD95 interacts with Stargazin, a transmembrane AMPA-R regulatory protein (TARP) that modulates AMPA-R properties (Turetsky, 2005; Ben-Yaacov et al., 2017).

So far, investigations of LGI1 function have been focused mainly on AMPA-R regulation to understand the mechanisms leading to epileptic seizures when LGI1 function is disturbed. Immunostaining studies on the hippocampus of *Lgi1*-KO mice have found a significant decrease of the GluA1 subunit expression (Ohkawa et al., 2013). In addition, electrophysiological studies performed on hippocampal slices from *Lgi1*-KO mice have confirmed the alteration of glutamatergic currents when LGI1 was altered (Fukata, 2006; Lovero et al., 2015). Indeed, *ex vivo* recordings of glutamatergic currents on hippocampal slices from wild-type (WT) mice have shown that an addition of LGI1 increased AMPA-R currents (Fukata, 2006), whereas a deletion of LGI1 decreased AMPA-R currents (Lovero et al., 2015). Moreover, transfection of LGI1 on hippocampal slices from KO mice allows to restore AMPA-R currents (Lovero et al., 2015). However, a previous study investigating the synaptic transmission in *Lgi1*-KO mice has failed to demonstrate any post-synaptic effect (Boillot et al., 2016) when synaptic transmission was monitored before the epileptic status was installed.

This regulation of AMPA-R is quite intriguing. Indeed, AMPA-R are involved in synaptic excitatory transmission (Sheng and Lee, 2001), and LGI1-alteration diseases are characterized by epileptic seizures translated into neuronal network hyperexcitability. Although most studies have agreed on an action of LGI1 on AMPA-R, the decrease of AMPA-R expression when LGI1 function is impaired is quite unexpected and in contradiction with the hyperexcitability observed during epileptic seizures. Up until now, this contradiction remains unexplained, but two hypotheses have been proposed to explain this result. First, the reduction of AMPA-R expression in the absence of LGI1 could be due to the homeostatic regulation following the kv1.1 channels downregulation (Seagar et al., 2017). Second, the hyperexcitability of the neuronal network associated with a downregulation of AMPA-R would probably affect more the inhibitory network. This would decrease the inhibitory transmission (Ohkawa et al., 2013). Nevertheless, none of these hypotheses have been demonstrated. Recently, the specific nano-organization of AMPA-R into clusters at the surface of synapses has been shown to be more relevant in synaptic transmission than the overall expression of AMPA-R at the surface of neurons. (Nair et al., 2013; Choquet and Hosy, 2020). Future studies are required to clarify the role of LGI1 on AMPA-R regulation and, more specifically, it would be interesting to investigate the role of LGI1 on the specific organization of AMPA-R at the synapses.

5. Effect of human LGI1 auto-antibodies

5.1. Polyclonal Abs effects

Besides the pathogenicity of LGI1 Abs and their major role in the disease, they can be used as tools to study LGI1 function and structure. As studies investigating the consequences of LGI1 genetic alteration on neuronal network regulation, LGI1 Abs action on synaptic transmission has also been investigated (Ohkawa et al., 2013; Petit-Pedrol et al., 2018). In accordance with findings of studies using transgenic mice (Fukata, 2006; Lovero et al., 2015; Ohkawa et al., 2013), a decrease of total and synaptic AMPA-R subunits and Kv1.1 channels has also been observed in the hippocampus of a mouse model with chronic intraventricular infusion of LGI1 Abs (Petit-Pedrol et al., 2018). Moreover, LGI1 Abs did not change mEPSC amplitude in CA1 area (Petit-Pedrol et al., 2018). The authors have also reported an increase of presynaptic release probability in dentate gyrus but not in CA1 (Petit-Pedrol et al., 2018) in accordance with studies using transgenic models (Boillot et al., 2016; Lovero et al., 2015).

Even if the effects of LGI1 Abs infusion are not as impressive as genetic modifications, the use of LGI1 Abs turns out to be effective, as this method allows to study LGI1 function on synaptic transmission with a spatio-temporal control and without genetic modulation. Moreover, infusion of Abs during adulthood avoids the developmental troubles reported in transgenic mice (Fukata et al., 2010) making the infused mouse model a very suitable model to understand LGI1-ADAM22 trans-synaptic complex.

5.2. Monoclonal Abs effects

Recently, several studies aiming at better understanding the mode of action of LGI1 Abs have highlighted the polyclonal nature of patient Abs by identifying both LRR-reactive Abs and EPTP-reactive Abs (Table 2) (Kornau et al., 2020; Ramberger et al., 2020). On the one hand, EPTP-

Table 2
Summary of EPTP and LRR domain function (Adapted from Kornau et al., 2020; Ramberger et al., 2020).

	EPTP mAbs	LRR mAbs
Mode of action	Competing with ADAM22 for LGI1 target	Prevent LGI1 homodimerization
Structural effects	Prevent LGI1-ADAM22 interaction	Caused LGI1-ADAM22 internalization
Localisation after a cerebroventricular infusion	Positive in serum Negative in immunostaining	Negative in serum Positive in immunostaining
Behavioral test (object recognition)	No effect	No effect
LTP Effect (CA3-CA1 synapses)	Strong reduction	Reduction
Neurotransmitters release	No effect on PPF	No effect on PPF
Kv1.1 expression	Strong expression reduction	Moderate expression reduction
AMPA–R expression	No alteration of mEPSC	Increase amplitude of mEPSC
Neuronal excitability	No effect	Increase neuronal excitability

Abbreviations: mAbs, monoclonal antibodies; LTP, long term potentiation; PPF, paired-pulse facilitation; mEPSC, miniature excitatory post-synaptic currents.

reactive monoclonal Abs (mAbs) have been produced (LGI1-EPTP-mAbs) and shown to bind LGI1 and to prevent LGI1 interaction with ADAM22 or ADAM23, leading to an absence of staining in the tissue (Kornau et al., 2020; Ohkawa et al., 2013; Yamagata et al., 2018). On the other hand, it has been observed that LRR-reactive mAbs (LGI1-LRR-mAbs) could bind to tissues and cell cultures, and trigger the internalization of the LGI1-ADAM22 complex (Ramberger et al., 2020). A decrease in Kv1.1α level in the hippocampus after LGI1-EPTP-mAbs injection has been observed using western-blot (Ramberger et al., 2020). A smaller decrease in Kv1.1α level has also been observed following LGI1-LRR-mAbs infusion. Nevertheless, only high levels of LGI1-LRR-mAbs brain infusion caused physiological effects *in vivo* in mice, these effects consisted in an alteration of novel object recognition (Ramberger et al., 2020). Moreover, an acute injection of mAbs in the CA3 area induced a strong alteration of LTP at CA3-CA1 synapses for both mAbs (Ramberger et al., 2020). Nevertheless, no effect has been observed on paired-pulse facilitation with LRR or EPTP mAbs injection (Ramberger et al., 2020). Additionally, in another study, hippocampal organotypic slices have been incubated for 24 h to 48 h with either LRR or EPTP-reactive mAbs and the excitability of neurons in CA3 area has been recorded by patch-clamp: an increased excitability was observed with reactive mAbs targeting both LRR and EPTP domains, the effect was bigger following LGI1-LRR-mAbs incubation (Kornau et al., 2020). Furthermore, LGI1-LRR-mAbs also caused a reduction in rheobase whereas EPTP-LRR-mAbs did not (Kornau et al., 2020).

These results are very interesting, since they describe two pathogenic populations of LGI1 Abs with different mechanisms of action in patients with autoimmune LE, potentially leading to slightly different symptoms. Thus, future studies should investigate AMPA-R and continue to deepen the understanding of Kv1.1 alteration. Moreover, most studies have been focusing on LGI1-ADAM22 interaction to explain pathogenic mechanisms (Ohkawa et al., 2013) but it is now clear that the LRR domain of LGI1 is also essential for the proper functions of the LGI1 complex.

6. Conclusion and futures directions

In this review, we exposed how LGI1 synaptic functions are disrupt in ADLTE and LE diseases and we highlighted the importance of clarifying LGI1 functions in the CNS to better understand the mechanisms underlying synaptic organization and synaptic transmission. Patients with ADLTE and LE suffer from severe cognitive deficits which can persist after treatment. Thereby, understanding the cause of these diseases is necessary to improve diagnostic and to offer adaptive treatments for these pathologies. More precisely, in LE the mechanism leading to an immune tolerance breakdown are still unclear. Futures studies should investigate the blood brain barrier in LE to highlight how LGI1 Abs can be produced in the CSF. Investigating these mechanisms will allow to better understand other diseases involving an immune tolerance breakdown such as multiple sclerosis.

Another important field of research is to understand the processes by which LGI1 dysfunction leads to epileptic seizures. The various approaches detailed in this review revealed that LGI1 protein plays an essential role in the formation and functioning of the network during development (Zhou et al., 2009; Fukata et al., 2010; Boillot et al., 2016) while, as observed in patient with LE, mainly synaptic functions are impacted during adulthood (Ohkawa et al., 2013; Petit-Pedrol et al., 2018). Previous studies highlighted a role of LGI1 in the regulation of synaptic transmission by kv1.1 channels (Schulte et al., 2006; Petit-Pedrol et al., 2018; Lancaster et al., 2019) and AMPA-R (Fukata, 2006; Fukata et al., 2010; Ohkawa et al., 2013; Lovero et al., 2015; Petit-Pedrol et al., 2018). Nevertheless, how these proteins are downregulated when there is a dysfunction of LGI1 is still unclear. LGI1 form a trans-synaptic complex which regulates presynaptic and postsynaptic organization including many synaptic proteins (Fukata et al., 2021). Futures studies should investigate the function of LGI1-ADAM22 trans-synaptic complex on the synaptic nano-organization. To reach this goal, a better knowledge of protein interactions with the LGI1-ADAM22 complex is required, as well as of the potential role of LGI1 outside the synapse. Moreover, there is a need to understand the mechanisms linking LGI1 with kv1.1 channels and AMPA-R. In particular the role of LGI1 in the regulation of the surface expression and trafficking of kv1.1 channels and AMPA-R has not yet been studied. In addition, Understanding regulation mechanisms of kv1.1 channels and AMPA-R will be relevant for the comprehension of other neurological diseases involving alterations of these proteins such as episodic ataxia type 1 (D'Adamo et al., 2020).

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Declaration of Competing Interest

The authors report that there is no conflict of interest.

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