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Imbalance of glutamatergic and GABAergic neurotransmission in audiogenic seizure-susceptible L*eucine-rich glioma-inactivated 1* (*Lgi1*)-mutant rats

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ABSTRACT

Leucine-rich glioma-inactivated 1 (*LGI1*) was identified as a causative gene of autosomal dominant lateral temporal lobe epilepsy. We previously reported that *Lgi1*-mutant rats carrying a missense mutation (L385R) showed audiogenic seizure-susceptibility. To explore the pathophysiological mechanisms underlying Lgi1-related epilepsy, we evaluated changes in glutamate and GABA release in *Lgi1*-mutant rats. Acoustic priming (AP) for audiogenic seizure-susceptibility was performed by applying intense sound stimulation (130 dB, 10 kHz, 5 min) on postnatal day 16. Extracellular glutamate and GABA levels in the hippocampus CA1 region were evaluated at 8 weeks of age, using *in vivo* microdialysis techniques. Under naïve conditions without AP, glutamate and GABA release evoked by high-K^+ depolarization was more prominent in *Lgi1*-mutant than in wild-type (WT) rats. The AP treatment on day 16 significantly increased basal glutamate levels and depolarization-induced glutamate release both in *Lgi1*-mutant and WT rats, yielding greater depolarization-induced glutamate release in *Lgi1*-mutant rats. On the other hand, the AP treatment enhanced depolarization-induced GABA release only in WT rats, and not in *Lgi1*-mutant rats, illustrating reduced GABAergic neurotransmission in primed *Lgi1*-mutant rats. The present results suggest that enhanced glutamatergic and reduced GABAergic neurotransmission are involved in the audiogenic seizure-susceptibility associated with *Lgi1*-mutation.

1. Introduction

Epilepsy is a chronic disease characterized by recurrent unprovoked seizures associated with neural hyperexcitation, affecting about 1% of the population worldwide [1]. Although epilepsy-related mutations are often located in genes of ion channels and

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ligand-gated channels, diverse pathogenic mutations in genes encoding non-ion channel proteins have also been identified [2]. Among them, heterozygous mutations of *Leucine-rich glioma-inactivated 1* (*LGI1*) were first reported to cause autosomal dominant lateral temporal lobe epilepsy (ADLTE, OMIM 600512), an inherited epileptic syndrome characterized by partial seizures with predominant auditory symptoms (e.g., auditory auras and seizure-susceptibility to specific sounds) [3–5].

Lgi1 is a neural secreted protein highly expressed in the central nervous system, especially in the hippocampus and neocortex [6]. Lgi1 interacts with a disintegrin and metalloproteinase (ADAM) family (e.g., ADAM22 and ADAM23) and post synaptic density protein 95 (PSD-95), and this interaction regulates the function of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors and voltage-gated K^+ (Kv) 1.1 channels in synapses [7–11]. Moreover, auto-antibodies against LGI1 have been detected in patients with autoimmune limbic encephalitis presenting with frequent seizures and memory deficits [12–14]. However, the mechanisms underlying Lgi1-related epilepsy remain elusive.

We previously developed a rat model that carries a missense mutation (L385R) of the *Lgi1* gene with ENU (*N*-ethyl-*N*-nitrosourea) mutagenesis [15]. This mutation impaired Lgi1 secretion, which was similar to the most of missense mutations responsible for ADLTE [15]. Furthermore, the *Lgi1*-mutant rats showed seizure-susceptibility to sound stimuli, sharing similarity with the clinical features of ADLTE [15–17]. Namely, *Lgi1*-mutant rats, which received acoustic priming (AP) treatments (130 dB, 10 kHz, 5 min) on postnatal day (P) 16, showed generalized tonic-clonic seizures (GTCSs) following wild running behaviors (sensitized startle responses) by acoustic test stimulation (130 dB, 10 kHz, 1 min) at 8 weeks of age. However, primed wild-type (WT) rats only exhibited wild running behaviors with the test stimulation, but no GTCSs [15–17]. In addition, we showed that astrocytic inwardly rectifying K^+ (Kir) 4.1 channels, which regulate the clearance mechanism of excessive extracellular K^+ (spatial K^+ buffering) and glutamate transport into astrocytes [18–20], were down-regulated in the *Lgi1*-mutant rats, suggesting that alterations in extracellular K^+ and/or glutamate levels are involved in audiogenic epileptogenesis [17,21].

In this study, we evaluated synaptic glutamate and GABA release in the hippocampus, which expresses a high density of *Lgi1* [6,22], using audiogenic seizure-susceptible *Lgi1*-mutant rats to explore the mechanisms underlying the pathogenesis of Lgi1-related epilepsy.

2. Materials and methods

2.1. Animals and ethical approval

F344-*Lgi1*^{m1Kyo} rats (NBRP Rat No. 0656) with a heterozygous missense mutation (L385R/+) by *N*-ethyl-*N*-nitrosourea (ENU) mutagenesis techniques were provided by the National BioResource Project-Rat (NBRP-Rat, http://www.anim.med.kyoto-u.ac.jp) [15]. The animals were bred and maintained according to the animal care methods complying with the Guide for the Care and Use of Laboratory Animals of the Ministry of Education, Science, Sports and Culture of Japan. All experimental procedures in this study were approved by the Animal Research Committee of Kyoto University and Osaka Medical and Pharmaceutical University (formerly Osaka University of Pharmaceutical Sciences). Only male animals were used for neurotransmission analyses.

2.2. Genotyping

F344-*Lgi1*^{m1Kyo} rats were mated with their WT littermates. DNA extracted from blood samples of rats on P15 was used for genotyping using a PCR-restriction fragment length polymorphism technique, as described previously [17]. Briefly, exon 8 including the mutation site was amplified by PCR using the Ampdirect Plus PCR buffer (Shimadzu, Japan). PCR products were digested with *Xsp* I (Takara Bio, Japan) and discriminated between mutant allele and wild-type allele using conventional agarose gel electrophoresis.

2.3. Acoustic priming (AP) treatments for audiogenic seizure generation

AP stimulation at P16 confers audiogenic seizure susceptibility *on Lgi1*-mutant rats, which evokes GTCSs with test stimulation at 8 weeks of age [17]. AP treatments for audiogenic seizure generation were performed using previously reported methods [15–17]. Briefly, animals were individually placed in a plastic cage (17 × 25 × 13 cm) within a larger sound-proof box and, after 1-min habituation, an intense AP stimulation (130 dB, 10 kHz, 5 min) was given by a loudspeaker (JBL Professional) placed centrally on the cover of the cage. Tone bursts were generated by a sound stimulator (DPS-725, Dia Medical System Co.) and amplified using a power amplifier (D75-A, Amcron). Non-primed animals were handled in the same manner described above, but no AP stimulation was delivered. All animals were then subjected to *in vivo* microdialysis studies at 8 weeks of age without receiving acoustic test stimulation.

2.4. In vivo microdialysis

Lgi1-mutant or WT rats at 7 weeks were anesthetized with pentobarbital (40 mg/kg, i. p.) and fixed in a stereotaxic instrument (Narishige, SR-6, Japan). A guide cannula was inserted into a position 1 mm above the hippocampus CA1 region (2.0 mm lateral and 3.8 mm caudal to the bregma, and 2.0 mm deep from the cortical surface) [23] and fixed to the skull with dental cement. After a recovery period of about one week, animals were subjected to *in vivo* microdialysis study, as previously reported [24]. A dialysis probe (Eicom, A-I-6-01, Japan) was inserted into the hippocampus CA1 region through a guide cannula and artificial cerebrospinal fluid (aCSF), containing NaCl 140 mM, KCl 2.4 mM, $MgCl_2$ 1.0 mM, $CaCl_2$ 1.2 mM, and $NaHCO_3$ 5.0 mM, was perfused at a flow rate of 1.5 μL/min using a microperfusion pump (Fig. 1A). High concentration K^+ (50 mM)-containing aCSF was perfused for 60 min to evaluate the depolarization-induced synaptic release. The dialysate samples were collected every 10 min. After experiments, animals were

deeply anesthetized with an intraperitoneal injection of pentobarbital (80 mg/kg) and the brain was removed from the skull. Then, 100-μm-thick coronal sections were prepared from each brain using a microslicer and the position of each injection site was checked.

2.5. Quantification of glutamate and GABA with HPLC

The dialysate samples were analyzed for glutamate and GABA levels using a HPLC-ECD system. Briefly, glutamate and GABA were derivatized with *o*-phthalaldehyde and separated on a cation exchange column (Eicom, 3.0 mm φ × 150 mm Eicompak SC-5ODS, Japan). The mobile phase consisted of 0.1 M phosphate buffer, 5 mg/L EDTA 2Na, pH 6.0, with 27% methanol pumped at a flow rate of 500 μL/min. The area under the curve for glutamate and GABA peaks were measured using eDAQ Power Chrom (eDAQ Pty Ltd., Australia). Extracellular glutamate and GABA values were quantified with external standard curves generated by four standard concentrations (10 nM, 100 nM, 1 μM, and 10 μM).

2.6. Statistical analysis

All data are expressed as the mean ± S.E.M. The significance of differences among multiple groups was determined by two-way ANOVA followed by Tukey's *post-hoc* test. A *P*-value of less than 0.05 was considered significant.

3. Results

In this study, *Lgi1*-mutant and WT rats were divided into two groups, respectively, according to whether they received AP stimulation (130 dB, 10 kHz, 5 min) on P16 as follows, non-primed *Lgi1*-mutant rats (n = 5), primed *Lgi1*-mutant rats (n = 5), non-primed WT rats (n = 6), and primed WT rats (n = 7). We then conducted *in vivo* microdialysis experiments at 8 weeks of age to evaluate extracellular glutamate and GABA levels in the hippocampal CA1 region (Fig. 1A). No animals were exposed to acoustic test stimulation to avoid behavioral influences (e.g., wild running or seizures) on glutamate and GABA levels.

Under naïve conditions without AP treatments, there was no difference in basal extracellular levels of glutamate or GABA between *Lgi1*-mutant and WT rats (Fig. 1B and C). However, high K^+ (50 mM)-induced release of both glutamate and GABA was significantly enhanced in *Lgi1*-mutant rats.

Treatments of animals with AP stimulation on P16 significantly elevated basal levels of glutamate both in *Lgi1*-mutant and WT rats (Fig. 2A and B). High K^+-induced glutamate release was also enhanced by AP treatments in both groups (Fig. 2A and B), yielding greater depolarization-induced glutamate release in *Lgi1*-mutant rats (Fig. 2C). In contrast, AP treatments did not affect basal GABA

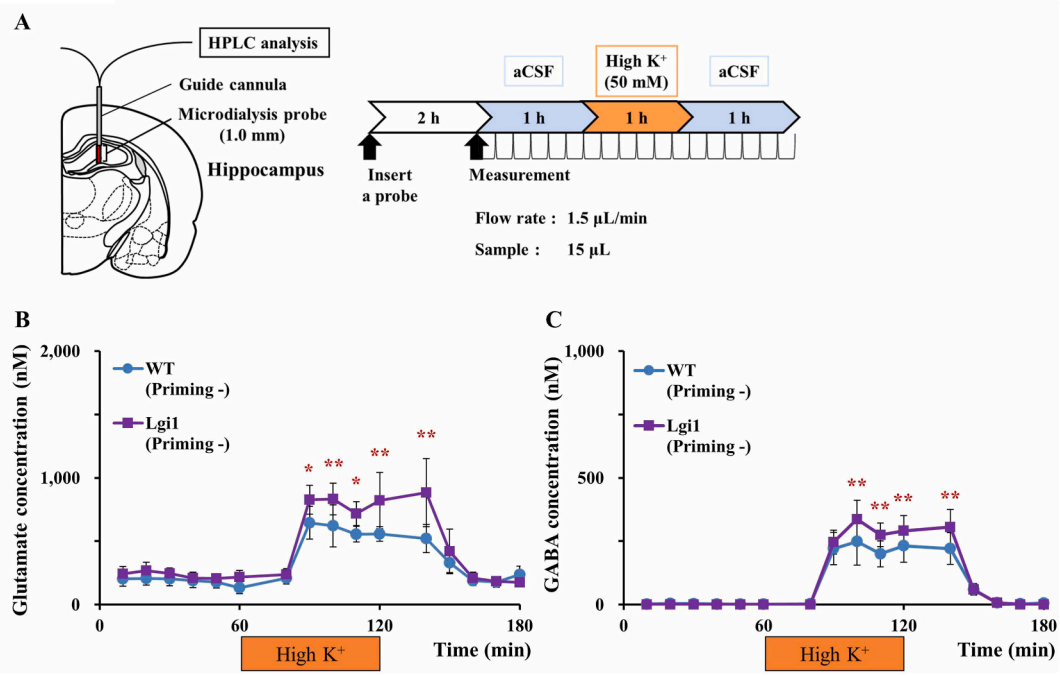

Fig. 1. Schematic overview and experimental flow chart of *in vivo* microdialysis techniques (A). Glutamate and GABA release in the hippocampus. Extracellular levels of glutamate (B) and GABA (C) were compared between wild-type (WT) rats and *Lgi1*-mutant rats. Depolarization stimulation involved applying high-concentration K^+ (50 mM)-containing artificial cerebrospinal fluid (aCSF) for 60 min through the dialysis probe. Each point represents the mean ± S.E.M. of 5 or 6 animals. **P* < 0.05, ***P* < 0.01, significantly different from WT group.

levels in *Lgi1*-mutant or WT rats (Fig. 3A and B). In addition, AP treatments significantly enhanced high K^+-induced GABA release only in WT rats, and not in *Lgi1*-mutant rats (Fig. 3A and B), illustrating that depolarization-induced GABA release was more prominent in WT than in *Lgi1*-mutant rats (Fig. 3C).

4. Discussion

Emerging evidence shows that the impairment of Lgi1, a secreted protein that regulates glutamatergic synaptic transmission, is associated with genetic and autoimmune epilepsy [5,10,11,14]. Here, we demonstrated for the first time that depolarization-induced synaptic release of glutamate and GABA markedly changed in *Lgi1*-mutant rats, a rat model of human ADLTE (summarized in Fig. 4A).

AP treatments given in the juvenile stage (P16) cause audiogenic excitatory behaviors (e.g., wild running and jumping) at a mature age (8 weeks of age) in WT rats. However, these animals rarely exhibit any convulsive seizures. In contrast, most animals carrying the

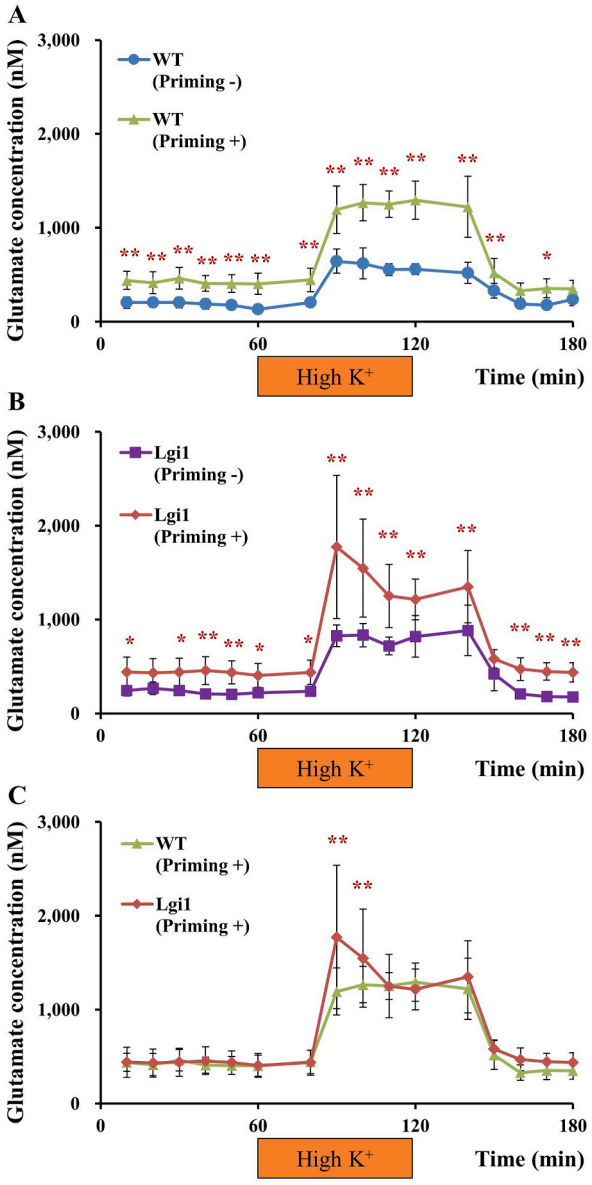

Fig. 2. Glutamate release in the hippocampus. Extracellular levels of glutamate were compared between non-primed wild-type (WT) and primed WT rats (A), non-primed *Lgi1*-mutant and primed *Lgi1*-mutant rats (B), and primed WT and primed *Lgi1*-mutant rats (C) (data from Fig. 1B redisplayed for comparisons between non-primed rats and primed rats). Depolarization stimulation involved applying high-concentration K^+ (50 mM)-containing artificial cerebrospinal fluid (High K^+) for 60 min through the dialysis probe. Each point represents the mean ± S.E.M. of 5–7 animals. $^*P < 0.05$, $^{**}P < 0.01$, significantly different from each other group.

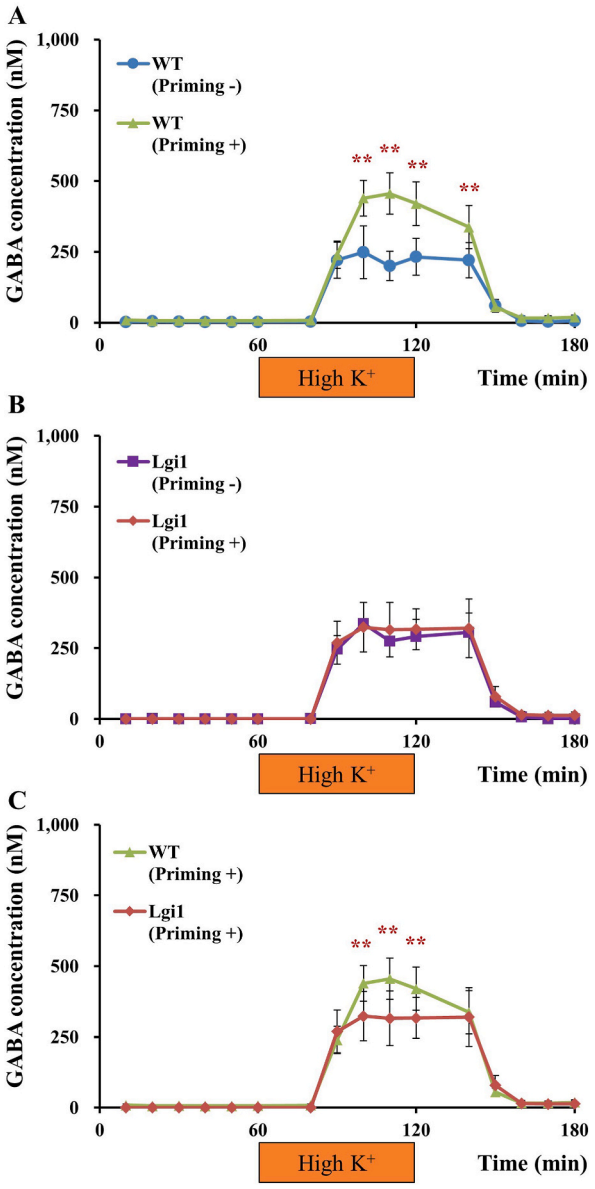

Fig. 3. GABA release in the hippocampus. Extracellular levels of GABA were compared between non-primed wild-type (WT) and primed WT rats (A), non-primed *Lgi1*-mutant and primed *Lgi1*-mutant rats (B), and primed WT and primed *Lgi1*-mutant rats (C) (data from Fig. 1C redisplayed for comparisons between non-primed rats and primed rats). Depolarization stimulation involved applying high-concentration K^+ (50 mM)-containing artificial cerebrospinal fluid (High K^+) for 60 min. Each point represents the mean ± S.E.M. of 5–7 animals. $^{**}P < 0.01$, significantly different from each other group.

loss-of-function mutation (L385R) develop GTCSs following wild running/jumping behaviors with acoustic test stimulation [15–17], suggesting that the dysfunction of Lgi1 facilitates audiogenic epileptogenesis. The present study demonstrated that AP stimulation applied on P16 significantly elevated basal levels of extracellular glutamate and enhanced depolarization-induced synaptic release of glutamate not only in *Lgi1*-mutant rats, but also in WT rats. Thus, developmental changes leading to hyper-excitation of glutamatergic neurotransmission may be involved in generation of audiogenic excitatory behaviors (e.g., wild running and jumping) after juvenile AP stimulation. On the other hand, depolarization-induced glutamate release in primed *Lgi1*-mutant rats was more prominent than in primed WT rats. In addition, although AP treatments also increased depolarization-induced GABA release in WT rats, this response to AP was abolished in *Lgi1*-mutant rats. Thus, the imbalance of excitatory/inhibitory neurotransmission, enhanced glutamate and reduced GABA synaptic release, in the hippocampus is supposed to cause more severe seizures such as GTCSs in *Lgi1*-mutant rats (Fig. 4B). Since LGI1-related glutamatergic transmission is reportedly involved in regulation of postsynaptic GABAergic interneurons in the hippocampus [10,11,25], dysfunction of Lgi1 might fail to activate GABAergic neurons.

A

	Basal		High K^+ evoked	
Glutamate	**WT**	***Lgi1***	**WT**	***Lgi1***
Priming (-)	–	–	–	↑
Priming (+)	↑	↑	↑	↑↑
GABA	**WT**	***Lgi1***	**WT**	***Lgi1***
Priming (-)	–	–	–	↑
Priming (+)	–	–	↑↑	↑

↑: increased, ↑↑; markedly increased

B

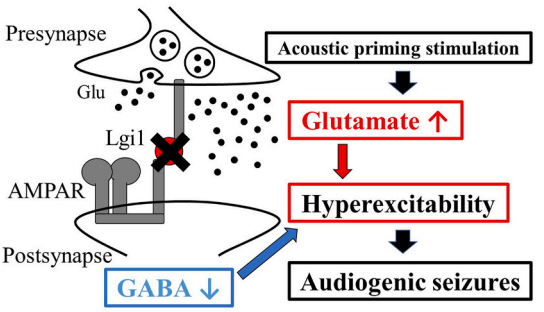

Fig. 4. Summarized results on hippocampal glutamate and GABA release in *Lgi1*-mutant rats (A) and schematic drawing on the imbalance of glutamatergic and GABAergic neurotransmission potentially linked to audiogenic seizure-susceptibility in *Lgi1*-mutant rats (B). Under naïve (non-primed) conditions, the *Lgi1*-mutation potentiated high K^+ depolarization-evoked glutamate and GABA release. On the other hand, acoustic priming (AP) stimulation (at P16) increased the basal glutamate level both in *Lgi1*-mutant and WT rats. It should be noted that, under primed condition, the *Lgi1*-mutation caused enhanced glutamate release and diminished GABA release during high K^+ depolarization (shown in yellow). This imbalance of glutamatergic and GABAergic neurotransmission in primed *Lgi1*-mutant rats may be involved in generation of audiogenic seizures associated with *Lgi1*-mutation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Even under naïve conditions without AP treatments, depolarization-induced glutamate and GABA release was more prominent in *Lgi1*-mutant rats than in WT rats. Our results on the enhancement of depolarization-induced glutamate release by the *Lgi1* mutation are consistent with the previous finding that truncated mutant Lgi1 increased the spine density and enhanced excitatory transmission [26]. Although the mechanism for the increase of evoked GABA release in *Lgi1*-mutant rats remains uncertain, this might be a compensatory response to the enhanced glutamate release.

While audiogenic seizures are reportedly associated with increased glutamate in the inferior colliculus and midbrain nucleus of the auditory pathway in other rodent models [27,28], we previously demonstrated that the hippocampus was one of the audiogenic seizure foci in *Lgi1*-mutant rats, where astrocytic Kir4.1 channels were significantly down-regulated during the development of epileptogenesis [16,17]. Astrocytic Kir4.1 channels mediate spatial K^+ buffering and glutamate uptake into astrocytes via EAAT1 and EAAT2 [18–21,29,30], playing a crucial role in the development of epilepsy [21]. Thus, down-regulation of Kir4.1 channels might at least partly be involved in the elevation of hippocampal glutamate level in *Lgi1*-mutant rats. In addition, we showed that the extracellular signal-regulated kinase (ERK) signaling pathway was activated by the inhibition of astrocytic Kir4.1 channels, which facilitated the secretion of brain-derived neurotrophic factor (BDNF) from astrocytes [31]. Since the development of audiogenic seizures and other epileptic seizures is known to be associated with increased BDNF-tropomyosin receptor kinase B (TrkB) signaling and ERK signaling [32–39], down-regulated Kir4.1 channels might also facilitate audiogenic epileptogenesis in *Lgi1*-mutation via the ERK/BDNF pathway. However, further studies are necessary to delineate the mechanisms underlying the interaction of Lgi1 with Kir4.1 channels and BDNF.

In conclusion, we analyzed synaptic release of glutamate and GABA in the hippocampus of *Lgi1*-mutant rats, where Lgi1 secretion was impaired [15]. The present study suggests that depolarization-induced synaptic release of glutamate was potentiated, but that of GABA release was diminished by the *Lgi1*-mutation. This imbalance of glutamatergic and reduced GABAergic neurotransmission may be involved in the audiogenic seizure-susceptibility associated with *Lgi1*-mutation. However, since the present results were obtained solely by *in vivo* microdialysis study, further analyses of functional changes by the *Lgi1*-mutation are necessary, especially the Lgi1 interaction with glutamate and GABA neurons using electrophysiological as well as immunohistochemical techniques, to delineate the mechanisms underlying Lgi1-related epilepsies.

Author contribution statement

Masato Kinboshi, Yukihiro Ohno: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Saki Shimizu, Kentaro Tokudome: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Tomoji Mashimo, Tadao Serikawa, Hidefumi Ito, Ryosuke Takahashi, Akio Ikeda: Analyzed and interpreted the data; Wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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