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Introduction of a Novel Molecular Mechanism of Epilepsy Progression: Roles of Growth Hormone Signaling in a Mouse Model of Temporal Lobe Epilepsy

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1. Introduction

Epilepsy is a chronic neurological disease involving recurring behavioral seizures, and affects approximately 1% of the worldwide population of humans and cats, and 2-3% of dogs. Epilepsy causes recurring behavioral seizures, which are transient behavioral changes caused by disordered, synchronized, and rhythmic firings of populations of neurons in the brain that propagate to regions connected with the first insult on the neural circuits, induced by abnormal neural plasticity (Browne and Holmes 2000). The seizure expression is induced by idiopathic/cryptogenic and remote symptomatic causes, as concrete examples, febrile illness in children younger than 16 years (Besli et al., 2010) and cerebrovascular and ethanol/drug-related accidents in adults. When the seizures are prolonged, or occur in a series, there is an increased risk of status epilepticus. About 15 % of persons with epilepsy experience status epilepticus, which induces more brain damage. It is known that large populations of epilepsy patients express status epilepticus due to medication changes in both children and adults. Hence, improving the compliance of patients to take medicine appropriately is very helpful to prevent the expression of status epilepticus.

Despite the importance of medication, more than one third of patients with epilepsy are estimated to have pharmacoresistant epilepsy (Browne and Holmes 2000). Half of patients with refractory epilepsy are characterized as having mesial temporal lobe epilepsy (TLE) with foci in the amygdaloid complex, hippocampus, and surrounding cortex. To solve the problem of pharmacoresistance, it is important to clarify the molecular mechanisms involved in the development of pharmacoresistant seizures. Additionally, patients with epilepsy are at high risk of developing anxiety, depression, learning disorders, and sudden death (Dodrill, 1986; Franks, 2003; Motamedi and Meador, 2003; Sillanpää and Shinnar, 2010). To improve the quality of life of patients, it is useful to clarify the comorbidity between seizures and other neuropsychiatry disorders. Depression and anxiety have the highest incidence in patients with TLE (Perini, et al., 1996). Hence, it should be clarified how the molecular signaling system regulates the development of pharmacoresistant abnormal neural plasticity and, as a result, recurring prolonged seizures that are induced by symptomatic causes. New drugs that can respond to seizures that known drugs fail to cure

should be developed based on the newly found signaling machinery. Many researchers have found molecular candidates responsible for seizure progression and the molecular mechanisms have been clarified little by little (Jia et al., 2011; Pitkänen and Lukasiuk, 2011). On the other hand, we have focused on clarification of the molecular mechanisms of epilepsy progression using a mesial TLE mouse model, amygdale kindled mice, showing epileptic seizures induced due to the development of abnormal neural plasticity in TLE regions. So far we have found three molecules responsible for epileptogenesis, a growth hormone, a sialyltransferase, and ganglioside GQ1b (Matsuhashi et al., 2003; Kato et al., 2008; Kato et al., 2009). The clarification of signaling mechanisms with these molecules will resolve the pharmacoresistancy and open a path for therapeutic intervention for cases of anxiety and depression in the near future.

2. Experimental animals

2.1 Introduction of experimental animal models

Several chronic models showing recurrent seizures have been developed as shown in Table 1.

Stimulant	Chronic recurrent seizures	References
Physical	kindling	Goddard et al., 1969; Racine et al., 1972; Kato et al., 2001
Chemical (metal)	alumina cream	Heinemann et al., 1986
	cobalt	Chang et al., 2004
	ferric iron	Willmore and Ueda, 2009
Chemical (drug)	pentylenetetrazol (Chronic schedule)	Schallier et al., 2009
	kainate	Antonucci et al., 2009
	pilocarpine	Pitkänen et al., 2011
Inherited	EL mice	Fueta et al., 1983
	DBA/2 mice (audiogenic)	Seyfried and Glaser, 1981
	SER rat	Hanaya et al., 2010
	Mongolian gerbil	Buchhalter 1993
	targeted gene-deficient mice	Puranam and McNamara, 1999; Meisleret al., 2001

Table 1. Species of epileptic model animals (especially rodents).

Physical (electro-stimulation): Kindling consists of the repeated administration of subconvulsive electrical stimulus to any of several brain regions, resulting in the development of EEG seizures (afterdischarges) and progressive behavioral seizures. When repeated stimuli are administrated into the amygdaloid complex and hippocampus, mesial temporal lobe epilepsy (MTLE), which is the cause in one-half patients with refractory epilepsy, is induced as eventual secondary generalized grand mal seizures. The kindling

model provides better insights into how abnormal neural plasticity is altered and newly acquired during epileptogenesis. Furthermore, when the number of grand mal seizures increases, status epilepticus is also caused in kindled mice. We therefore focused on kindling to clarify the molecular mechanisms of epileptogenesis and the occurrence of status epilepticus.

Chemical (metal): When alumina cream is applied to the cerebral cortex of monkeys and cats, chronic spontaneous seizures are induced, however, the seizures subside after several months to years (Heinemann et al., 1986). Investigating the mechanisms of the termination of seizure expressions might provide clues to end refractory epilepsy. Implantation of cobalt into the cerebral cortex easy induces focal and secondarily generalized seizures in rodents, however, cobalt metal causes a large area of cortex to be lost, while the hippocampus containing the dentate gyrus appears intact (Chang et al., 2004). Microinjection of ferric ions into the rodent brain results in chronic recurrent seizures, which are brain injury responses induced by hemorrhage and free radical reactions observed in human posttraumatic epilepsy (Willmore and Ueda, 2009).

Chemical (drug): Status epilepticus model mice are prepared with pentylenetetrazol (PTZ), kainate, and pirocarpin. PTZ-induced seizures: injection of PTZ (43 mg/kg) into the peritoneal cavity of 4-week-old mice 3 times per week for 4 weeks induced stereotyped spontaneous seizures (unpublished procedure). Kainate-induced seizures: an infusion of kainate (1 nmol/0.5 μl) into the hippocampus of 8-week-old mice induces status epilepticus about 20 days after infusion (unpublished procedure; Antonucci et al., 2009). Pirocapine-induced seizures: pirocarpine (100 mg/kg) is injected into the peritoneal cavity every 20 min until onset of status epilepticus (Elliott et al., 2003). SE induced with kainate and pirocarpine accompanies hippocampal damage, which seems to mimic human hippocampal atrophy. Additionally, the concentration of each drug should not be over the adequate dosage, as mice die immediately following the appearance of seizures.

Spontaneous and genetic manipulation: EL mouse: tonic-chronic seizures appear when a mouse is tossed to height of 10 cm 10 times a day for 2-3 weeks (unpublished procedure; Fueta et al., 1983). Audiogenic seizure model of DBA/2: audiogenic seizures appear when a 3-week-old mouse receives one 60-sec exposure to a pure tone sound (120 db) (Seyfried and Glaser, 1981). SER rat: rats homozygous for both zitter (zi) and tremor (tm) autosomal recessive mutations shows spontaneous epileptic seizures involving hippocampal atrophy in the CA3 subfield, in addition to many vacuoles in the brain (Hanaya et al., 2010). Gerbils with hypoplasia of the basilar artery circle suffer chronic seizures by a sudden change of circumstances (Buchhalter 1993). On the other hand, many one-gene-deficient mice have been produced with epileptic seizures, in which it is suggested that several channel gene deficient-dependent seizures mimic idiopathic seizures (Puranam and McNamara, 1999; Meisleret al., 2001).

2.2 Preparation of kindled mice

Figure 1 shows the dorsal side of the head (B) and the coronal section of the brain (C) in kindled mice with a microinjection cannula. All procedures were performed according to the guidelines for animal welfare of Osaka Prefecture University and Kyoto Sangyo University, and approved protocols. Surgical procedures were conducted under anesthesia with isoflurane (Dainippon Sumitomo Pharma Co. Ltd., Osaka, Japan) and Escain (Mylan Inc., Osaka, Japan) as described previously (Kato et al., 2001). Positions of brain regions were determined according to the stereotaxic coordinates shown by Paxinos and Franklin

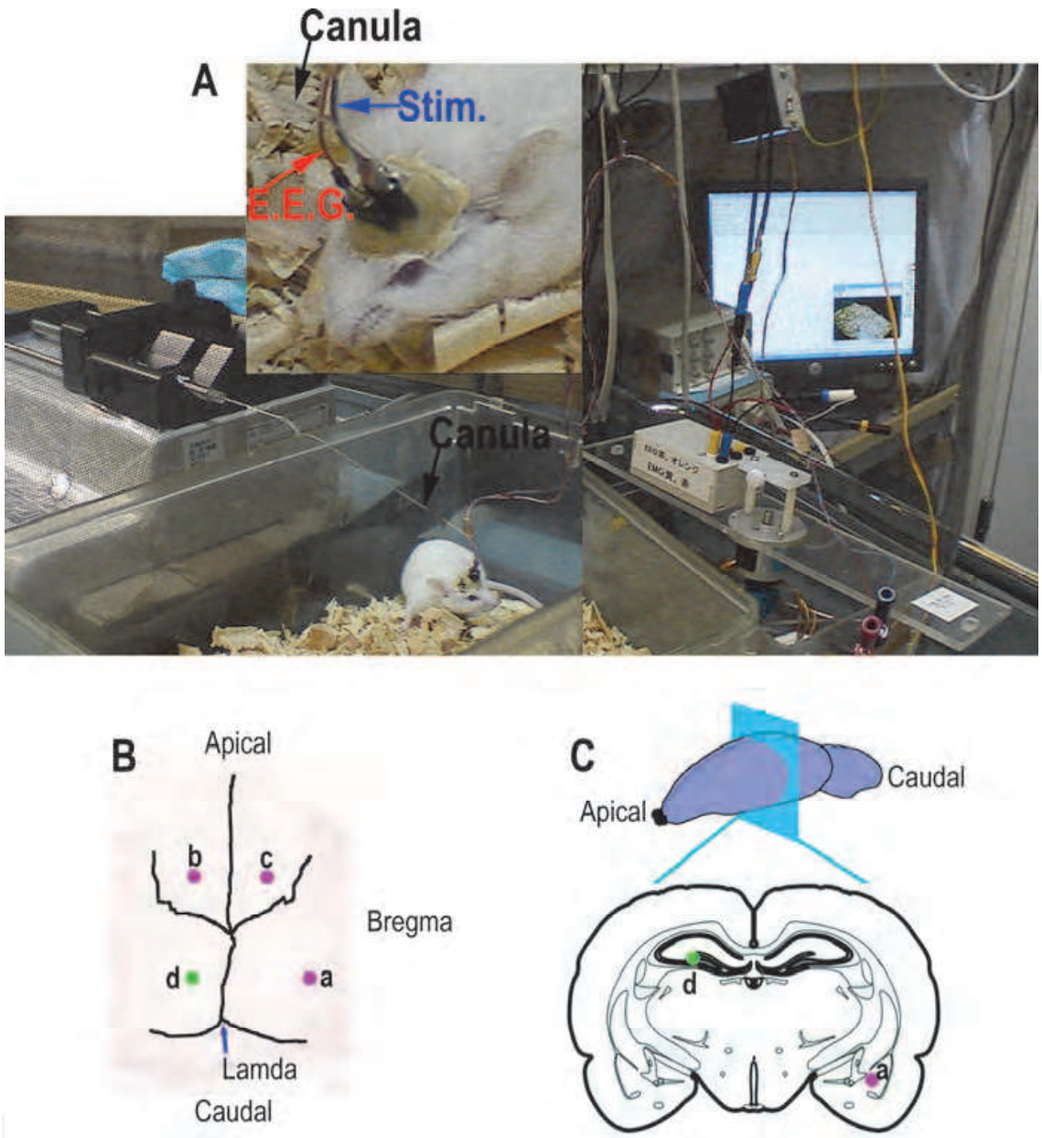

Fig. 1. Photos show free-moving mice receiving kindling stimulation, E.E.G. recording, and microinjection (A) and views showing positions of electrodes and microinjection cannula (B and C). Views showing the dorsal side of the head (left) and a coronal section of the brain (right) in kindled mice with a microinjection cannula (A). In (A), Stim., stimulation; E.E.G., electroencephalographic; cannula, microinjection cannula transplanted into the hippocampus.

(2001). Unipolar cathode electrode; made of tungsten steel and 0.1 mm in width (Inter Medical Co. Ltd., Nagoya, Japan), and an anode electrode; made of a screw and 1.0 mm in width and 3.0 mm in length (Biotex Kyoto, Japan), were implanted on the right side of the basolateral amygdaloid complex (A -2.0, L 3.0, V 4.5 mm from bregma; **a**) and on the left side of the subdural space (A 2.0, L 1.5 mm from bregma; **b**), respectively. Ten days after surgery, unrestrained conscious mice received a biphasic square wave pulse [480 μA; 60 Hz, 200 μs duration, for 2 sec] using an electrical stimulator (SEN-3301; Nihon Kohden, Tokyo,

Japan) and isolator (SS-202J) once a day. Electroencephalographic (EEG) recordings were carried out with bilateral electrodes of the subdural space (b and c) prior to and after stimulation using PreAmp and Head Amp (BEMCT-21 and BH-3, Low cut = 0.5, High cut = 30; Biotex, Kyoto, Japan) and the data acquisition program SleepSign ver.2.0 (Kissei Comtec Co. Ltd., Nagano, Japan). Seizures were monitored with a modified classification of Racine's criteria (Racine 1972) and the duration of afterdischarge and freezing was added to the behavioral criteria as described previously (Kato et al., 2001): stage 1, plus mouth and facial movement; stage 2, plus forelimb clonus and duration of afterdischarge greater than 5 sec; stage 3, plus forelimb clonus and duration of freezing greater than 15 sec; stage 4, plus tonic clonic seizures and tail up; stage 5, plus falling over. After reaching stage 5, mice were used in experiments as fully kindled mice following more stimulation for only 3 days. The brains of the mice were removed after decapitation within 2 hrs of the last kindling stimulation. The sham-operated mice were not stimulated but otherwise treated identically in all respects.

2.3 Microinjection of drugs into the brains

To observe the effect of drugs during epileptogenesis, a microinjection cannula (ID=0.2 mm; Eicom Corp., Kyoto, Japan) with a guide cannula (ID = 0.4 mm, OD = 0.5mm; Eicom Corp.) was also implanted on the left side of the hippocampus (A –2.0, L 1.5, V 2.5 mm; d in Fig. 1B and C) at the time of surgery to prepare kindled mice (Kato et al., 2009).

One microliter of genotropin (1 µl of 540 pmol/µl; Faizer, Tokyo, Japan), pegvisomant (90 pmol/µl, antagonist, Faizer) and buffer (40 mg/ml D-mannitol, 2 mg/ml glycine, and 0.02 mM sodium phosphate, pH 6.85); and 1 µl octreotide acetate (1 µl of 90 pmol/µl; Novartis, Tokyo, Japan) and buffer (45 mg/ml D-mannitol, 3.4 mg/ml lactic acid in NaHCO3, pH 4.5) were injected into the hippocampus of unrestrained conscious mice (d in Fig. 1B) at a flow rate of 0.5 µl /min using a microsyringe pump (KDS 200 series; KD Scientific) according to the schedule described in Fig. 3A, in which we administered drugs every other day 7 times in total before and during epileptogenesis, respectively. Concentrations of the drugs applied to mice were determined based on the weight of drugs per weight of human patients. Mice received a biphasic square wave pulse 30 min following the microinjection. Statistical tests were mainly performed using a combination of Excel and Statview-J 5.0. Additionally, one microliter each of genotropin octreotide acetate, and pegvisomant (antagonist, recombinant protein, 12 mg/ml; Pfizer) was injected into the hippocampus of respective mice without kindling stimulation. Pegvisomant was used to investigate whether it affected the functions of endogenous GH in the brain.

3. Differential expressions during epilepsy progression and following status epilepticus

Reports have indicated gene expression patterns during and following epileptogenesis and the development of status epilepticus induced in rodents with drugs and electro-stimulation (Nedivi et al., 1993; Tang *et al.*, 2002; Becker *et al.*, 2003; Elliott *et al.*, 2003; Lukasiuk *et al.*, 2003; Gorter *et al.*, 2006). They have found several promising new anti-epileptogenic targets, for example, previous studies have indicated common immediate early genes including SER-regulated genes (Becker *et al.*, 2003; Gorter *et al.*, 2006) and prostaglandin-endoperoxide synthase 2 (Ptgs2, Cox-2) (Gorter *et al.* 2006; Ristori *et al.* 2008) as candidates for genes

causative of epileptogenesis. While inhibition of Cox-2 reduces epileptiform bursting in the hippocampus slice (Ristori *et al.*, 2008), the inhibitor had no effect on epileptogenesis or spontaneous seizures *in vivo* (Holtman et al., 2009). This contradiction suggests that the roles of Cox-2 should also be studied in epilepsy. It was also reported that the expressions of hormone genes, such as galanin (Lerner et al., 2008; Mitsukawa et al., 2008), neuropeptide Y (Shannon and Yang, 2004; El Bahh *et al.*, 2005; Silva *et al.*, 2005), leptin (Shanley et al., 2002), and somatostatin (Monno *et al.*, 1993; Buckmaster *et al.*, 2002) were up-regulated in the brain following epileptogenesis and showed anti-epileptic effects. On the other hand, candidate genes associated with human epilepsy have been nominated in the HuGE database (Jia et al., 2011). More recent experimental research has shown the effect of antiepileptic drugs on differential gene expressions and antiepileptogenic behaviors (Pitkänen and Lukasiuk, 2011).

In the present review, we introduce growth hormone signaling as a candidate molecular system associated with epileptogenesis. We have screened differential gene expressions in the brain regions during kindling epileptogenesis by genechip array. As a result, we have identified growth hormone (GH), increasing the gene expression in the brain regions that kindling stimuli propagate from the basolateral amygdala during epileptogenesis (Fig. 2). On the other hand, the present amygdala kindled mice also indicated up-regulated expressions of SER-regulated genes (Kato et al., 2009) and the Cox-2 transcript (Fig. 4) following kindled seizures.

4. Research

4.1 Growth hormone signaling system

Differential expressions of the GH transcript that increases in the brain during and following kindling epileptogenesis (Fig. 2) have been confirmed using a quantitative real-time polymerase chain reaction-based analysis of mRNA (qRT-PCR) and Western blot analysis (Kato et al., 2009). Next, we investigated the distribution of the GH transcript in the brain to know whether the transcript is expressed in regions where the kindling-stimuli propagate in amygdala-kindled mice using *in situ* hybridization (Kato et al., 2009). Neuronal cells were typically oval with cRNA signals of GH in the regions, in which GH mRNA was expressed moderately in the brain, particularly around the limbic area containing the piriform cortex, the anterior thalamic nucleus, and the hippocampus. Previous studies of neural connections have already clarified that amygdala kindling leads more easily to the propagation of stimuli to the hippocampus→anterior thalamus→apical cortex involving the cingulate through neural connections (Meibach and Siegel 1977; Amaral and Witter 1995; Price 1995; Gemmell and O'Mara 2002). Thus, it was suggested that regions of the brain that express GH could be involved in the propagation of stimuli in neural circuits during epileptogenesis.

To compare mRNA levels, total RNA was prepared from the apical part of the cerebral cortex (yellow circle), thalamus, (green circle), and the caudal part of the cerebral cortex [which includes posterior hippocampus, amygdaloid complex, temporal lobe] (red circle) of kindled, intermediate stage 3, and sham-operated mice. GeneChip array shows up-regulation of GH transcript during epileptogenesis (A). Means and S.E.M. were calculated based on raw signal intensities (MG430_Scal_Signal) compensated by signal intensity with GAPDH control probes on the Mouse Genome 430 2.0 Array of the Affymetrix Genechip. There were significant differences of GH expression using Kruskal-Wallis tests of Kyplot 4.0:

in the apical cortex (x70.6, **p<0.01), the thalamus (x54.4, **p<0.01) and caudal cortex (x23.2, *<0.05) between sham-operated and full-kindled mice.

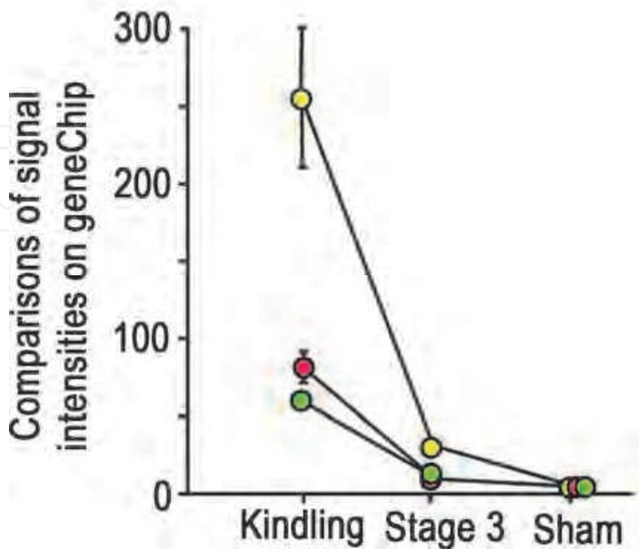

Fig. 2. Comparisons of expression levels of Gh between full-kindled, intermediate stage 3, and sham-operated mice using genechip array. To compare mRNA levels, total RNA was prepared from the apical part of the cerebral cortex (yellow circle), thalamus, (green circle), and the caudal part of the cerebral cortex [which includes posterior hippocampus, amygdaloid complex, temporal lobe] (red circle) of kindled, intermediate stage 3, and sham-operated mice. GeneChip array shows up-regulation of GH transcript during epileptogenesis (A). Means and S.E.M. were calculated based on raw signal intensities (MG430_Scal_Signal) compensated by signal intensity with GAPDH control probes on the Mouse Genome 430 2.0 Array of the Affymetrix Genechip. There were significant differences of GH expression using Kruskal-Wallis tests of Kyplot 4.0: in the apical cortex (x70.6, **p<0.01), thalamus (x54.4, **p<0.01), and caudal cortex (x23.2, *<0.05) between sham-operated and full-kindled mice.

To investigate whether GH has distinct roles in epileptogenesis, we injected genotropin (human GH recombinant, rGH) and octreotide, which is a somatostatin analog reducing secretion of GH (Lamberts 1987) into the hippocampus according to the schedule described in Fig. 3A. First, the administration of rGH resulted in a significant enhancement of epileptogenesis compared to the control as a whole (two-way factorial ANOVAs in Fig. 3C) and an increased number of spikes in afterdischarge following epileptic seizures (two-way factorial ANOVAs in Fig. 3B). Second, the progression of behavioral changes during epileptogenesis was attenuated (two-way factorial ANOVA in Fig. 3E); however, there were no differences in the number of spikes and duration of afterdischarges (Fig. 3D). This suggests that growth hormone causes the afterdischarge threshold to decrease during epileptogenesis.

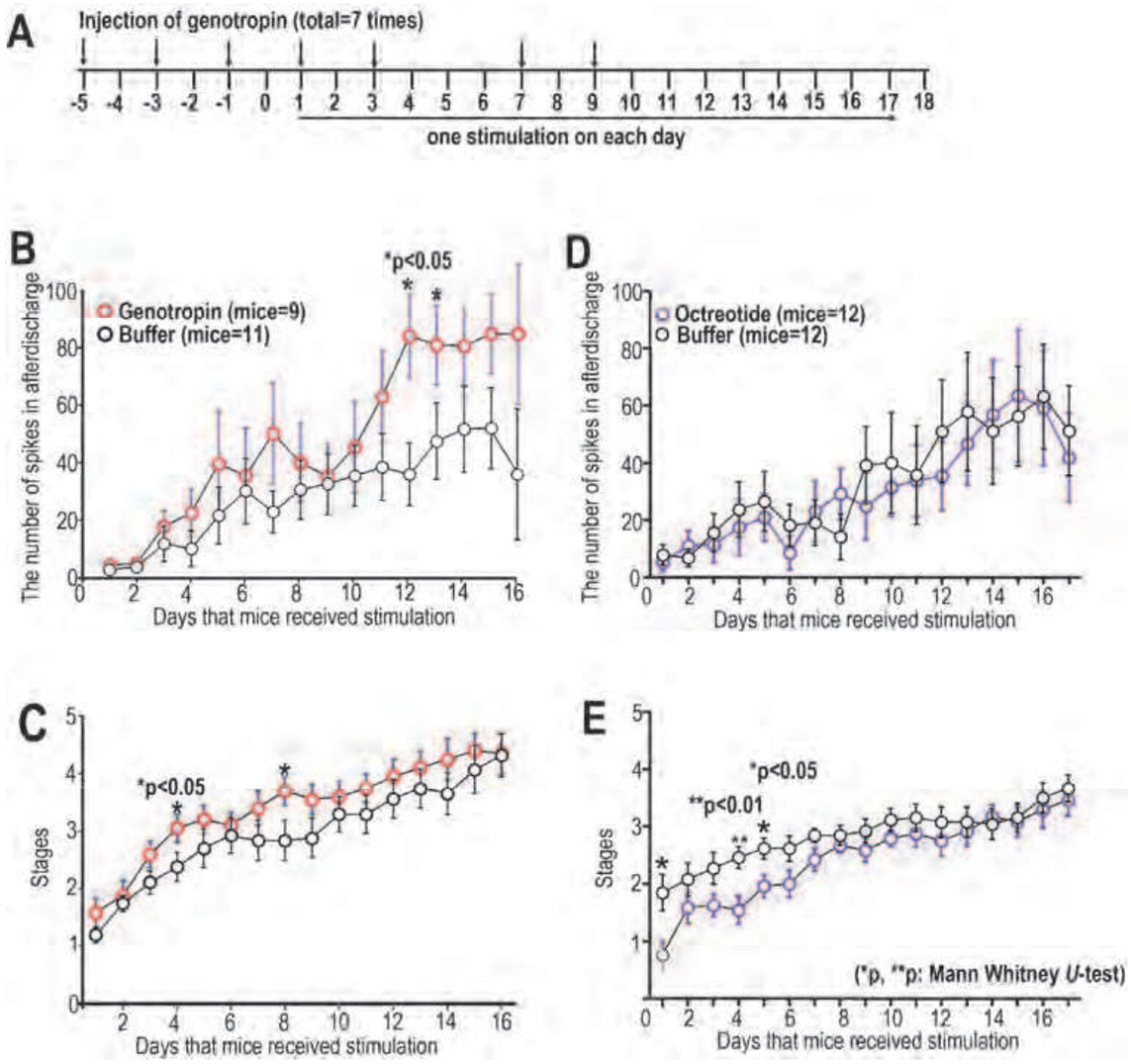

Fig. 3. Effect of genotropin and octreotide on epileptogenesis (adapted from Kato et al., 2009). Schedules of injection (A) of genotropin (1 ml of 540 pmol/ml, red circles in B and 4C), octreotide acetate (1 ml of 90 pmol/ml, blue circles in D and E), and their buffer (1 ml, black circles in B-E) or kindling stimulation are shown. Stimulation was started from number 1 and continued to the 17th day. The number of spikes in afterdischarges on electroencephalograms (EEGs) are shown (B and D). Transition of stages (C and D). Means and S.E.M. for the two characteristics of mice with or without drugs following stimulation on each day were evaluated with two-way factorial ANOVA, which showed differences in mice with or without in B to E (Kato et al., 2009). The data for days when mice received stimulation were compared between injections of drugs and the buffer (Mann-Whitney U-test: *p<0.05, **p<0.01). Administration of the hormone into the hippocampus markedly enhanced the progression of kindling, and the number of spikes during afterdischarges increased in mice following development of tonic-clonic convulsion. On the other hand, the administration of an inhibitor of its secretion into the hippocampus elicited a delay in progression.

As we have demonstrated the effect of GH on the brain during epileptogenesis, we next investigated whether the presence of GH induced GH signaling in the brain during epileptogenesis. As a method of investigation, we determined whether GH regulated the expressions of seizure-responsive genes directly in the brain. Finally, when the hippocampus was exposed to rGH for 24 hrs without kindling stimulation, rGH induced significant differential expressions of Egr1 mRNA (Kato et al., 2009), but not Cox-2 mRNA in the caudal cortex containing the hippocampus and amygdaloid complex (Fig. 4, result experimented by Mr. M. Suzuki). Both Egr1 and Cox-2 mRNAs were seizure-responsive genes in our kindling system. These relative results show that exogenous rGH induced an increase of Egr1 mRNA directly at least downstream of GH signaling, while Cox-2 transcripts were not regulated by GH signaling. It has been reported that Cox-2 inhibitor

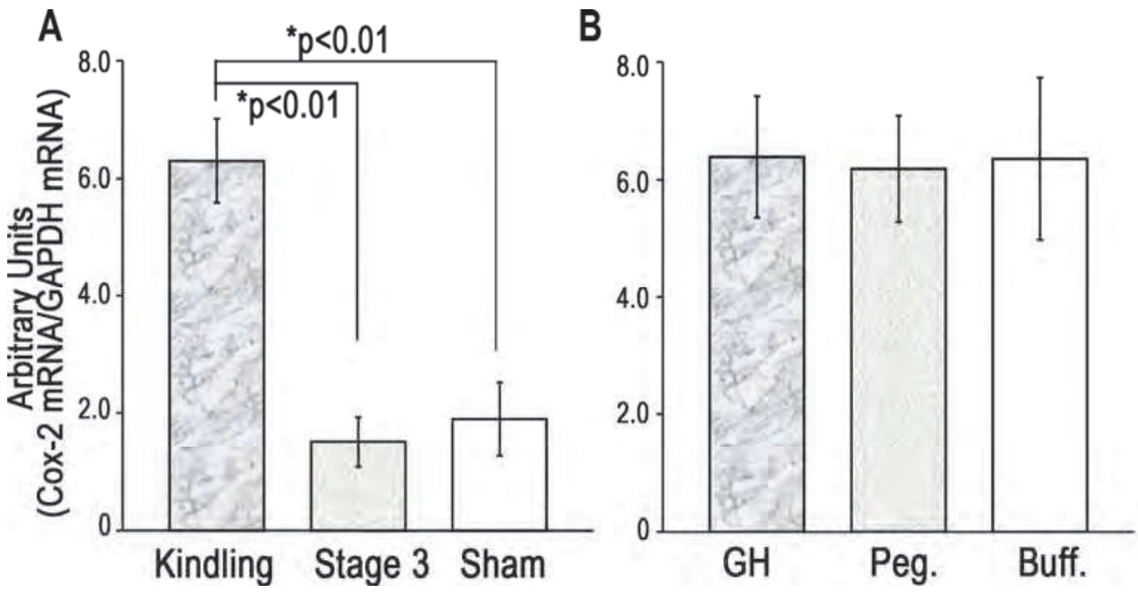

Fig. 4. Effects of kindled seizures (A) and rGH microinjections (B) on expression levels of Cox-2 (prepared by M. Suzuki). Isolation of RNA and real-time RT-PCR followed the methods described previously (Kato et al., 2009). Quantitative PCR of Cox-2 mRNA was performed with SYBR Green (Power SYBR Green PCR Master Mix, Applied Biosystems) using a 7300 Real-Time PCR system. Primer pairs used for the PCR were: 5'- GAT CAT CAA TAC TGC CTC AA -3'/5'-CAG CTC AGT TGA ACG CCT TT-3' (Cox-2, 184 bp, 1729-1912bp in NM_011198). The bar graph (mean + S.E.M.) shows the ratio of Cox-2 mRNA relative to GAPDH mRNA between sham-operated (n=10), stage 3 (n=8), and full-kindled (n=10) mice in the cerebral cortex containing the hippocampus and amygdala using the Kruskal-Wallis test [Steel-Dwass test]: *p<0.001, [kindling/stage 3 (between kindling and stage 3), *5p<0.01; kindling/sham, *4p<0.01]. Another bar graph shows the ratio of these transcripts in the caudal part of the cerebral cortex containing the hippocampus and amygdala with the administration of rhGH (n=4), pegvisomant (n=4), and the buffer (n=4) using the Kruskal-Wallis test: p=0.981. There was no difference in Cox-2 transcripts among drug administrations.

has little effects on epileptogenesis or spontaneous seizures (Holtman et al., 2009), which also suggests that Cox-2 does not function under GH signaling.
GH regulates physiological processes, including carbohydrate and lipid metabolism as well as somatic growth and development, therefore, it is possible that epileptogenesis is correlated with the differential expression of carbohydrates and lipids. Next, we screened the differential expression of gangliosides during epileptogenesis.

4.2 Effect of ganglioside expressions

A crude ganglioside mixture was prepared with extracts of the hippocampus dissected from adult mice following kindled seizures, and high performance thin-layer chromatography (HPTLC) analysis was performed according to previous reports (Iwamori and Nagai, 1981). The signal intensity of each ganglioside developed on the HPTLC plate was calculated in individual mice (6 kindled and 6 sham-operated mice) using PDquest software (Bio-rad,Tokyo, Japan) and analyzed using a combination of Excel and Statview-J 5.0. The analysis demonstrated a decrease of GM1 and increase of GQ1b following kindled seizures (Kato et al., 2008). The increase of GQ1b in the hippocampus following kindled seizures was confirmed by immunofluorescence with anti-GQ1b antibody. Taken together, the level of endogenous GQ1b increased following seizures in amygdaloid kindled mice, suggesting that the contents of GQ1b in the hippocampus are subject to epileptogenesis regulated by GH signaling.

5. Conclusion

We first found that GH plays distinct roles in epileptogenesis in the limbic system of the brain via GH signaling. While it was reported that GH is involved in lipolysis and has an effect that opposes that of insulin in the peripheral tissues (Scacchi *et al*., 2003), the present kindled seizures up-regulated the expressions of GQ1b in the brain. Given that 2-deoxy-D-glucose (2DG) increases the afterdischarge threshold (Garriga-Canut *et al.* 2006) and the present kindled-seizures cause up-regulation of the expressions of an enzyme related to carbohydrate transition, α2,3-sialyltransferase (ST3Gal IV), in the hippocampus and thalamus (Okabe *et al*., 2001; Matsuhashi *et al*., 2003). Hence, we propose that metabolic regulation by GH signaling adjusts the afterdischarge threshold during epileptogenesis. We have developed ST3Gal IV gene-deficient mice and are studying the involvement of ST3Gal IV in epileptogenesis. The relevance of GH signaling, sialylation, and lipid metabolism in the progress of epilepsy should be clarified in the near future.

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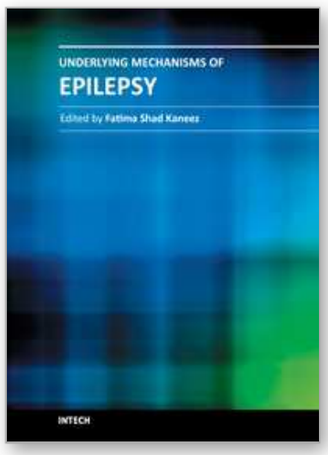

Underlying Mechanisms of Epilepsy

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This book is a very provocative and interesting addition to the literature on Epilepsy. It offers a lot of appealing and stimulating work to offer food of thought to the readers from different disciplines. Around 5% of the total world population have seizures but only 0.9% is diagnosed with epilepsy, so it is very important to understand the differences between seizures and epilepsy, and also to identify the factors responsible for its etiology so as to have more effective therapeutic regime. In this book we have twenty chapters ranging from causes and underlying mechanisms to the treatment and side effects of epilepsy. This book contains a variety of chapters which will stimulate the readers to think about the complex interplay of epigenetics and epilepsy.

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