

Postnatal interleukin-1 β administration after experimental prolonged febrile seizures enhances epileptogenesis in adulthood

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Abstract It remains unclear whether prolonged febrile seizures (pFS) in childhood facilitate mesial temporal lobe epilepsy (MTLE) in adulthood. Interleukin (IL)-1 β is associated with seizures in children and immature animal models. Here, we use a rat model of pFS to study the effects of IL-1 β on adult epileptogenesis, hippocampal damage, and cognition. We produced prolonged hyperthermia-induced seizures on postnatal days (P) 10–11 and administered IL-1 β or saline intranasally immediately after the seizures. Motor and cognitive functions were assessed at P85 using rotarod and passive avoidance tests. Electroencephalogram recordings were conducted at P90 and P120. Hippocampal CA1 and CA3 neurons and gliosis were quantified at the end of the experiment. Spontaneous seizure incidence was significantly greater in rats that had received IL-1 β than in those that had received saline or those without hyperthermia-induced seizures ($p < 0.05$). Seizure frequency did not differ significantly between the three groups and no motor deficits were observed. Passive avoidance learning was impaired in rats that received IL-1 β compared with controls ($p < 0.05$), but was not different from that in rats that received saline. Hippocampal cell numbers and gliosis did not differ between the three groups. These results indicate that neuronal loss and gliosis are not prerequisites for the epileptogenic process that follows pFS. Our results suggest that infantile pFS combined with IL-1 β overproduction can enhance adulthood epileptogenesis, and might contribute to the development of MTLE.

Keywords Febrile seizure · Cytokine · Mesial temporal lobe epilepsy · Cognition · Hippocampus · Passive avoidance

Introduction

Some patients with mesial temporal lobe epilepsy (MTLE) have a history of prolonged febrile seizures during childhood, and a few prospective studies have reported the development of MTLE in children with febrile status epilepticus (Tanabe et al. 2011; Lewis et al. 2014). In experimental studies, prolonged hyperthermia-induced seizures (pHS) in developing rats are associated with elevated electroclinical seizure susceptibility in adulthood, with or without hippocampal cell injury (Dubé et al. 2000, 2006; Fukuda et al. 2014).

Interleukin (IL)-1 β has acute and long-lasting effects on neuronal excitability. The -511C/T polymorphism in the *IL1B* gene is associated with sporadic development of simple febrile seizures (Kira et al. 2005). IL-1 β receptor-deficient immature mice are resistant to hyperthermia-induced seizures (Dubé et al. 2005), and administration of IL-1 β increases hyperthermic seizure susceptibility in developing rats (Fukuda et al. 2009). Furthermore, prenatal stress enhances infantile drug-induced febrile seizures as a result of enhanced IL-1 β release (Qulu et al. 2012). With respect to long-lasting effects, it was reported that upregulation of the IL-1 β -microRNA-146a axis, a mediator of inflammation, is associated with seizures in children and immature animal models and might facilitate later epileptogenesis (Omran et al. 2012). Pre-exposure to lipopolysaccharide on postnatal day (P) 14 enhances seizure susceptibility in a number of rat models, which is reversed by IL-1 receptor antagonism, and produces a long-lasting, tumor necrosis factor α -dependent increase in in vitro hippocampal excitability (Auvin et al. 2010; Galic et al.

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2008). Furthermore, repetitive postnatal pHS combined with IL-1 β administration in rats enhances adulthood kainic acid-induced seizures with mild hippocampal neuronal injury, implicating IL-1 β in the development of MTLE in humans (Fukuda et al. 2014).

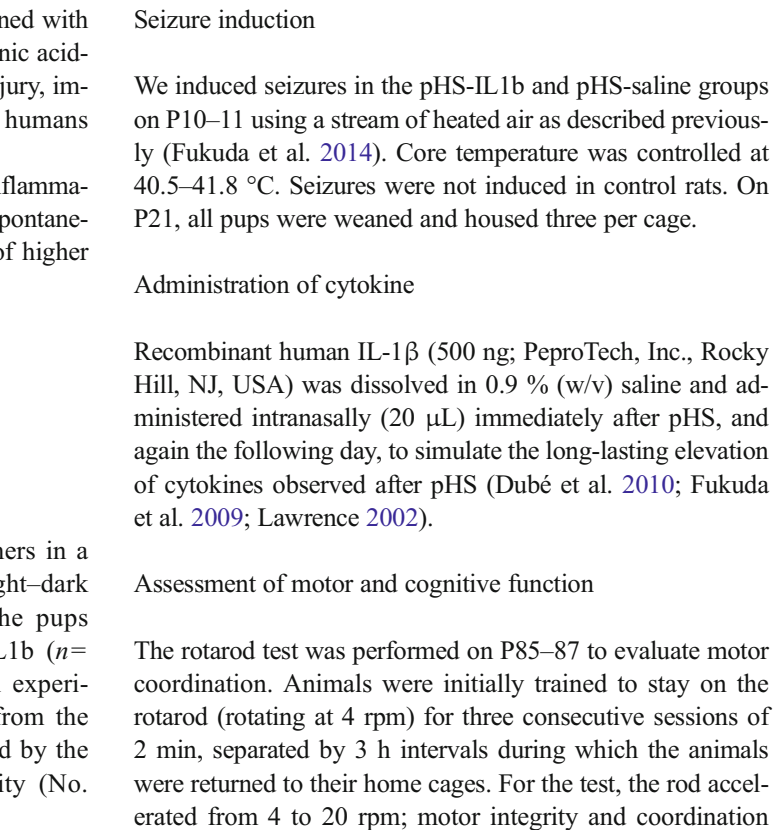
Here, we test the hypothesis that elevation of proinflammatory cytokines after pHS in infantile rats enhances spontaneous seizures, neuronal cell injury, and disturbance of higher brain functions in adulthood.

Materials and methods

Animals and experimental grouping

Lewis rats were born and housed with their mothers in a quiet, temperature-controlled room on a 12 h light–dark cycle, with food and water freely available. The pups were assigned to three groups (Fig. 1a): pHS-IL1b ($n=14$); pHS-saline ($n=16$); and control ($n=15$). All experimental procedures conformed to the guidelines from the Ministry of Education of Japan and were approved by the animal experimental committee of our University (No. TE-17-2).

Fig. 1 Experimental design and EEG findings. **(a)** Schematic showing the timescale of pHS induction, developmental IL-1 β administration, and behavioral and histological tests in adulthood. **(b)** Representative EEG showing sporadic interictal events in the hippocampus, and spontaneous electrographic seizures recorded from hippocampal electrodes, consisting of polyspikes or sharp-wave trains that spread to the cortex



were assessed over four trials as the mean latency from the beginning of the trial until the rat fell from the rotarod.

The passive avoidance paradigm began the next day to evaluate learning and memory. Each rat was placed individually in the illuminated chamber, and upon entry into the dark chamber received electric shocks (100 V, 1.0 A, 2 s) twice to the feet through the floor grid. Rats were immediately returned to the home cage. The following day, the rats were placed into the same illuminated chamber and the interval between placement into the apparatus and entry into the dark compartment (step-through latency) was recorded, with a cut-off time of 300 s.

Assessment of seizure activity

After the passive avoidance test, rats were anesthetized with pentobarbital (25 mg/kg i.p.) and silver electroencephalogram (EEG) electrodes were implanted in the left hippocampus (AP -4.0 , L 3.5 , V 3.5 mm relative to bregma) and cortex (over the left occipital cortex). After 3–4 days' recovery, long-term EEG recordings and visual observation were carried out over two separate 4 h sessions (6–10 p.m.) at P90–95 and P120–125 (Fig. 1a). Electrographic seizures were defined as events consisting of polyspikes or sharp waves (amplitude > twofold background) that lasted more than 6 s (Dubé et al. 2010).

Hippocampal neuron quantification and evaluation of gliosis

After EEG monitoring, rats were deeply anesthetized with pentobarbital and killed by cervical dislocation. Brains were removed, perfused with 4 % (w/v) paraformaldehyde, and embedded in paraffin for sectioning. Using a microtome, 10 μ m coronal sections were cut from the septal area where the two blades of the dentate are equal in size and form a V shape (2.8 mm posterior to bregma), to a point 3.3 mm posterior to bregma. Every 10th section was stained with cresyl violet, and cell counts were performed in the pyramidal cell layers of CA1 and CA3 (defined as described previously; Fukuda et al. 2014) of the right hippocampus by two investigators who were blind to the experimental grouping. Neurons were included when the nucleus and nucleolus were clearly identifiable.

Every 20th section was used for glial fibrillary acidic protein (GFAP) staining. Sections were deparaffinized, rehydrated and washed; endogenous peroxidase was quenched with 3 % (v/v) hydrogen peroxide in water. Sections were incubated overnight at 4 °C with goat anti-GFAP polyclonal primary antibody (Chemicon, Temecula, CA, USA). The following day, the sections were incubated with the secondary antibody, HRP-conjugated rabbit anti-goat IgG (Dako Japan, Co., Ltd. Kyoto, Japan) for 3 h at room temperature. Staining was visualized using diaminobenzidine (Dako). The area of GFAP staining was measured in CA1 and CA3 using Adobe Photoshop CS4 Extended (Adobe Systems, San Jose,

CA) and ImageJ 1.47 (Wayne Rasband, National Institute of Health, Bethesda, ML, USA).

Statistical analysis

Data were analyzed using a one-way ANOVA followed by Scheffe's multiple comparisons test for parametric data; the Kruskal–Wallis test followed by Dunn's test for nonparametric data; or χ^2 followed by Bonferroni's test (SPSS version 20; SPSS Japan, Tokyo, Japan). Values are expressed as the mean \pm S.E. and $p < 0.05$ was considered significant.

Results

Prolonged hyperthermia-induced seizures in developing rats

Hyperthermia was maintained for 30 min after seizure onset (40.2 ± 0.2 °C), and total seizure duration was 20–24 min. The maximum core temperature during hyperthermia was 41.9 ± 0.3 °C. All rats showed stereotyped seizures, consisting of facial automatisms and repetitive sudden arrests of hyperkinesia during hyperthermia. These movements were occasionally followed by body flexion and loss of posture control, and sometimes clonic convulsions.

Assessment of adulthood seizure activity

Electrographic seizures recorded from hippocampal electrodes consisted of polyspikes or sharp-wave trains (Fig. 1b). Behavioral correlates of these seizures were sudden cessation of activity with or without facial automatisms. The incidence of spontaneous seizures was significantly greater in pHS-IL1b rats (35 %) than in pHS-saline rats (6 %) and control rats (0 %) ($p < 0.05$) (Fig. 2a). There was no significant difference between the two pHS groups in the number of seizures per hour (pHS-IL1b, 0.4 ± 1.0 ; pHS-saline, 0.02 ± 0.1 ; Fig. 2b) or their duration (pHS-IL1b, 12 ± 3 s; pHS-saline, 9 s; Fig. 2c).

Assessment of brain function and pathology

In the passive avoidance test, step-through latency in the pHS-IL1b group (median, 220 s; range 5–360 s) was significantly shorter than in the control group (360 s; $p < 0.05$), but was not different from that in the pHS group (median, 300 s; range, 72–360 s; Fig. 3b). The rotarod test did not reveal any significant differences in performance between the three groups (pHS-IL1b, 44 ± 4 s; pHS-saline, 56 ± 4 s; control, 51 ± 4 s; Fig. 3a). In the hippocampus, no differences were observed between the three groups in the number of neurons in the CA1 (pHS-IL1b, 49 ± 1 ; pHS-saline, 45 ± 1 ; control, 44 ± 2) or CA3 (pHS-IL1b, 42 ± 2 ; pHS-saline, 39 ± 2 ; control, 39 ± 2 ; Fig. 4a–

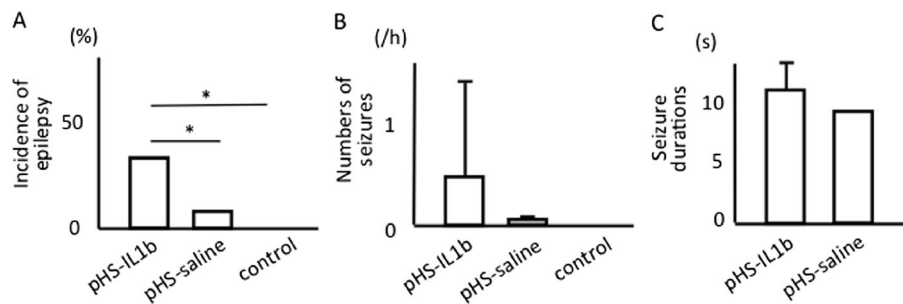


Fig. 2 Incidence, number and duration of EEG seizures. (a) Epilepsy incidence was higher in rats in the pHS-IL1b group than in the pHS-saline and control groups. (b) Number of seizures per hour was not

significantly different between the pHS-IL1b and pHS-saline groups. (c) Seizure durations were not different between the pHS-IL1b and pHS-saline groups. $*p < 0.05$

c). Similarly, the GFAP-immunopositive area was not significantly different between the three groups in the CA1 (pHS-IL1b, $1.4 \pm 0.2 \times 100 \mu\text{m}^2$; pHS-saline, $1.2 \pm 0.2 \times 100 \mu\text{m}^2$; control, $1.5 \pm 0.1 \times 100 \mu\text{m}^2$) or CA3 (pHS-IL1b, $1.7 \pm 0.2 \times 100 \mu\text{m}^2$; pHS, $1.3 \pm 0.2 \times 100 \mu\text{m}^2$; control, $1.5 \pm 0.1 \times 100 \mu\text{m}^2$).

Discussion

Our study is the first to use the infantile pHS model to study the effects of IL-1 β on adult epileptogenesis. We have shown that IL-1 β administration after postnatal pHS enhances epileptogenesis and impairs cognitive function in adulthood.

Reports using rodents have identified a relationship between seizure susceptibility in adulthood and pretreatment with lipopolysaccharide or IL-1 β (Fukuda et al. 2009; Lee et al. 2012), but few studies have examined the influence of proinflammatory cytokines in the infantile brain on adulthood epileptogenesis after prolonged neonatal febrile seizures, either in animals or in humans. Intranasal administration of 500 ng recombinant human IL-1 β is sufficient to significantly elevate IL-1 β protein concentrations in the frontal lobes of immature rats to 288 pg/mg (range, 222–534) (Fukuda et al. 2009), hence a 500 ng dose of IL-1 β was considered appropriate for the present study.

It was previously reported that pHS in developing rats induced long-lasting endogenous IL-1 β production in the hippocampus, and that *de novo* synthesis of IL-1 β was induced for at least 24 h before declining to control levels (Dubé et al. 2010). However, in a study of children with prolonged febrile seizures or acute encephalitis/encephalopathy, IL-1 β concentrations in cerebrospinal fluid were elevated only in the patients with encephalitis/encephalopathy (from <4.0 to 45 pg/mL) and not in those with febrile seizures (Ichiyama et al. 1998). A genetic predisposition to IL-1 β hyperproduction in patients who experience prolonged febrile seizures, however, may be important for subsequent epileptogenesis in adulthood. Indeed, the -511C/T polymorphism in the *IL1B* gene, which is related to a hyperproduction of IL-1 β , is associated with development of MTLE (Kanemoto et al. 2003).

The mechanisms of action of IL-1 β are numerous, including increasing blood–brain barrier permeability, inhibiting γ -aminobutyric acid (GABA)-mediated Cl^- flux, promoting angiogenesis, and inhibiting or delaying the release of IL-1RA (an endogenous IL-1 antagonist) (Ravizza et al. 2011; Vezzani and Granata 2005; Vezzani et al. 2008). Early-life elevation of IL-1 β via maternal or neonatal infection results in complex, long lasting changes in inflammatory cytokines in the neocortex, hippocampus, and serum (Arrode-Bruses and Bruses 2012; Garay et al. 2012), which may underlie increases in adulthood seizure susceptibility (Galic et al. 2009). Furthermore, IL-1 β is thought to affect the function of N-methyl-D-

Fig. 3 Cognitive and motor evaluation. (b) Step-through latency in the passive avoidance task was significantly shorter in the pHS-IL1b group than in the control group, but not the pHS group. (a) Latency to fall from the rotarod was not different between the three groups. $*p < 0.05$. Data are median and range (b) or mean \pm SE (a)

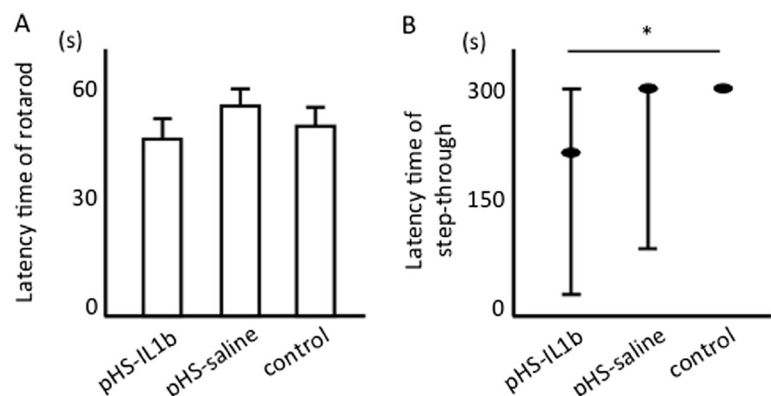
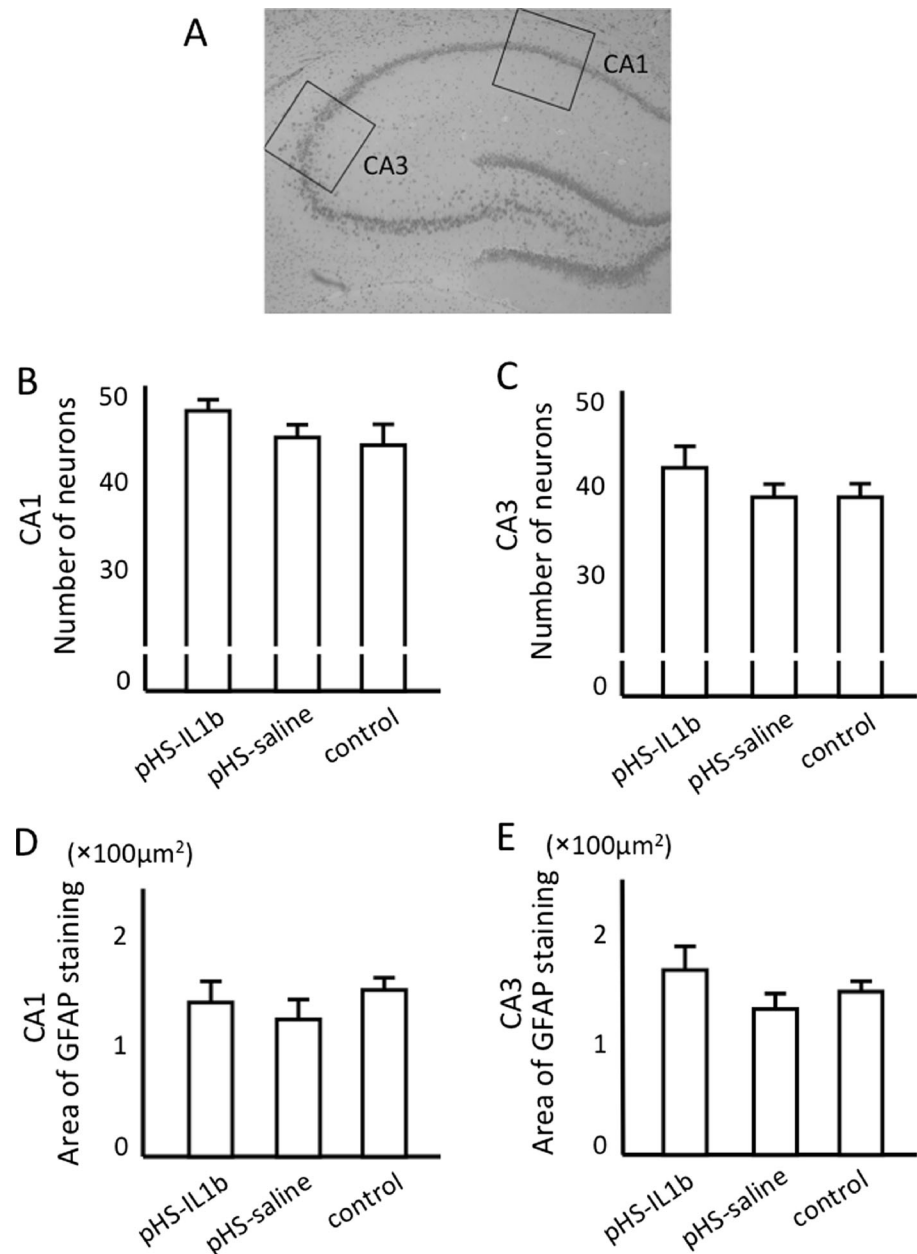


Fig. 4 Neuronal counts and astrogliosis. **(a)** 250,000 μm^2 areas delineated for pathological analysis of the CA1 and CA3 pyramidal cell layers. **(b, c)** Neuronal cell counts were not different between groups. **(d, e)** GFAP-immunopositive staining was not different between groups. Data are presented as means \pm S.E



aspartate (NMDA) receptor agonists, and NMDA receptor function is important in the pathogenesis of both febrile seizures and MTLE in humans (Viviani et al. 2003). IL-1 β enhances NMDA receptor-mediated Ca^{2+} currents in rat hippocampal pyramidal neurons (Viviani et al. 2003) and is involved in kindling progression (Ravizza et al. 2008). Kindling epileptogenesis is associated with activation of the IL-1 β system in astrocytes, likely triggered by the repetitive epileptogenic stimulation of the hippocampus (Ravizza et al. 2008). Another study indicated that an NMDA receptor blocker suppresses hyperthermia-induced seizures and their kindling in developing rats (Morimoto et al. 1995). Together, this evidence indicates that the enhanced adulthood epileptogenesis observed in the pHS-IL1b group in our study was a result of

enhanced kindling induced by the action of IL-1 β on NMDA receptors, and that endogenous IL-1 β might exert its epileptogenic effects in children with febrile seizures via NMDA receptor activation. Future experiments will examine the expression patterns and function of NMDA receptors in adult rats with developmental IL-1 β exposure.

In the passive-avoidance test, step-through latency was shorter in the pHS-IL1b group than in the control group, but was not significantly different from that in the pHS-saline group. It is possible that seizure activity before the passive avoidance test might bias the test in the learning paradigm and this may have contributed to the high variance in the pHS-IL1b group. Seizure monitoring should therefore be performed before cognitive testing.

Although memory impairment in MTLE is reported to correlate with the degree of hippocampal sclerosis (Cendes et al. 2012), and gliosis is a recognized characteristic of epileptic tissue (Pitkanen and Sutula 2002; Sharma et al. 2007), we found no abnormalities in hippocampal cell number or gliosis, consistent with previous findings in rats (Fukuda et al. 2014; Lee et al. 2012). However, hippocampal specimens obtained from surgically treated MTLE patients revealed five distinct neuropathological subgroups, one of which shows no significant pathological changes (Blümcke et al. 2007). Therefore, the pHS-IL1b group in our study may represent that specific MTLE subtype, indicating that significant hippocampal pathology is not a prerequisite for the epileptogenic process that follows febrile status epilepticus.

A limitation of our study is the lack of a fourth group, intranasal IL-1 β without prior pHS. However, this condition was examined in a previous study, in which it was found that IL-1 β alone has no significant influence on adulthood susceptibility to drug-induced seizures (Fukuda et al. 2014). This indicates that endogenous IL-1 β hyperproduction in the developing rat is not in itself enough to influence epileptogenesis in adulthood.

In the present study, the incidence of epilepsy in the pHS-saline group was 6 %. This figure is remarkably consistent with data obtained cohort studies investigating the incidence of subsequent epilepsy in children with febrile seizures (Shorvon and Goodridge 2013). This similarity highlights the validity of the pHS model as a tool for the study of infantile febrile seizures.

In conclusion, we have shown that postnatal pHS and an excess of IL-1 β enhances epileptogenesis in adulthood. Our results indicate that prolonged febrile seizures in childhood, coupled with IL-1 β overproduction, may contribute to the development of MTLE.

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All experimental procedures conformed to the guidelines from the Ministry of Education of Japan and were approved by the animal experimental committee of our University. This article does not contain any studies with animals performed by any of the authors.

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