UC Irvine
UC Irvine Previously Published Works

Title

Febrile seizures: mechanisms and relationship to epilepsy.

Permalink

https://escholarship.org/uc/item/04z8c2gg

Journal

Brain & development, 31(5)

ISSN

0387-7604

Authors

Dubé, Céline M
Brewster, Amy L
Baram, Tallie Z

Publication Date

2009-05-01

DOI

10.1016/j.braindev.2008.11.010

Copyright Information

Peer reviewed

Febrile seizures: Mechanisms and relationship to epilepsy

Céline M. Dubé[a], **Amy L. Brewster**[a], and **Tallie Z. Baram**[a,b,*]

a*Department of Anatomy and Neurobiology, University of California Irvine, Irvine, CA 92697-4475, USA*

b*Department of Pediatrics, University of California, Irvine (UC Irvine), Med. Sci. I, ZOT: 4475, Irvine, CA 92697-4475, USA*

Abstract

Studies of febrile seizures have been driven by two major enigmas: first, how these most common of human seizures are generated by fever has not been known. Second, epidemiological studies have linked prolonged febrile seizures with the development of temporal lobe epilepsy, yet whether long or recurrent febrile seizures cause temporal lobe epilepsy has remained unresolved. To investigate these questions, a model of prolonged (complex) febrile seizures was developed in immature rats and mice, permitting mechanistic examination of the potential causal relationships of fever and seizures, and of febrile seizures and limbic epilepsy. Although the model relied on hyperthermia, it was discovered that the hyperthermia-induced secretion of endogenous fever mediators including interleukin-1β, which contributed to the generation of these 'febrile' seizures. In addition, prolonged experimental febrile seizures provoked epilepsy in a third of the animals. Investigations of the mechanisms of this epileptogenesis demonstrated that expression of specific ion (HCN) channels and of endocannabinoid signaling, may be involved. These may provide novel drug targets for intervention in the epileptogenic process.

Keywords

Fever; Epileptogenesis; Animal models; Seizures; Hippocampus; Ion channels; Inflammation; Development

1. Introduction

Febrile seizures (FS), generally defined as seizures taking place during fever, and without an obvious central nervous system (CNS)-invasive infection, are the most common type of convulsive events in infants and young children [1]. FS lasting less than 10 [2,3] or 15 min [4] have not been associated with subsequent epilepsy or cognitive deficits in prospective or retrospective studies [5–7]. However, the consequences of prolonged FS, one of the forms of complex FS, are controversial [2,8]. Retrospective studies have linked a history of prolonged FS and subsequent temporal lobe epilepsy (TLE) [9–12]. However, prospective studies failed to implicate prolonged FS as a strong candidate for causing TLE [13].

If prolonged FS are responsible for TLE, then a strong incentive exists for preventing them. Prevention of these seizures would benefit from an understanding of the means by which fever leads to seizure generation. This need to understand the pathophysiology of FS, and the controversy over the clinical outcome of prolonged FS have provided an incentive for the

*Corresponding author. Address: Department of Pediatrics, University of California, Irvine (UC Irvine), Med. Sci. I, ZOT: 4475, Irvine, CA 92697-4475, USA. Tel.: +1 949 824 1131; fax: +1 949 824 1106. *E-mail address*: E-mail: tallie@uci.edu (T.Z. Baram).

development of animal models for these seizures. Such models enable direct examination of the potential mechanisms for the generation and consequences of these seizures, using a panoply of investigational tools.

2. How does fever generate seizures?

Febrile seizures occur in a strongly age-specific manner, supporting the strong contribution of factors that selectively characterize specific stages of brain development [14,15] (see Table 1 for the mechanisms of febrile seizures generation). The seizures are familial in some cases and sporadic in others, suggesting that both genetic and environmental elements contribute to their generation [16]. The contribution of environment, namely the increase in brain temperature (hyperthermia) to seizure generation, has become evident from the use of animal models, where hyperthermia leads to seizures in practically all rats or mice. This suggests that genetic susceptibility is not necessarily required for induction of such seizures [17–20]. Conversely, the fact that different mouse strains vary in the temperature required to generate seizures (seizure-threshold temperature; [21]), strongly implies that the genetic background may influence the susceptibility to developing a seizure with fever (although when the temperature is high enough, all tested strains develop seizures).

Several genes have been implicated in the susceptibility to febrile seizures, including those coding sodium channels, [22,23], $GABA_A$ receptors [24–26], and interleukins [27,28]. In addition, interactions among several genes might contribute to the occurrence of these seizures in a more complex manner.

Elevating brain temperature in itself alters many neuronal functions, including several temperature-sensitive ion channels [29,30]. This should influence neuronal firing and the probability of generating massive synchronized neuronal activity, i.e., seizures. Remarkably, hyperthermia provoked by medication overdose or hot baths often provoke seizures in young children [31], indicating that increase in brain temperature may suffice to generate seizures. Obviously, fever involves, in addition to increased brain temperature, also an inflammatory process including secretion of cytokines in the periphery as well as in the brain [32,33]. Indeed, it was discovered that fever and hyperthermia share common mechanisms to provoke seizures: The fever-promoting, pyrogen, interleukin-1β contributes to fever generation and, conversely, fever leads to the synthesis of this cytokine in hippocampus [34–37]. In addition, interleukin-1β, has been shown to increase neuronal excitability, acting via both glutamate and GABA [38]. *In vivo*, these actions of interleukin-1β enhance the actions of seizure-provoking agents [38]. In support of an important role for endogenous interleukin-1β in the generation of febrile seizures has come from studies in mice lacking the receptor for this cytokine. Much higher temperatures were required to elicit hyperthermic seizures in these mice [21], and interleukin-1β provoked seizures in immature rats and mice when given directly into the brain [21]. In addition, using lipopolysaccharide (LPS), a bacterial toxin, to induce release of endogenous interleukin-1β 1 in rodents lowers the threshold to kainic acid, and combining LPS with low-dose kainic acid results in seizures [39,40].

It might be noted that fever of specific infectious etiologies, and specifically HHV6 might influence the probability of generation of febrile seizures [41,42]. Finally, hyperthermia-induced hyperventilation and alkalosis have been proposed as a pivotal element of febrile seizure generation (see elsewhere in this issue). As discussed more fully elsewhere [43], alkalosis of the brain has been shown to provoke neuronal excitability [44,45], and contributes to seizure pathophysiology in models where the latency between fever and seizure onset is long (30 min; [46]). Remarkably, human conditions associated with severe alkalosis, including prolonged crying and pyloric stenosis of infants, are not associated with the generation of seizures.

3. What kind of seizures are induced by fever?

In children, a large behavioral spectrum of seizure is provoked by fever. Classical febrile seizures are short and lack motor phenomena that point to a focal origin. In other words, simple febrile seizures do not involve movements restricted to a single or unilateral limbs. However, in children, the onset of febrile seizure may not be recognized prior to the evolution of motor movement, so that subtle early components of the seizures may be missed (See Neville BG, elsewhere in this issue). Specifically, behavior arrest, confusion, dazed look or altered consciousness may be missed. These may point to origins of the seizures in the limbic system – the brain region most susceptible to seizures.

In rodent models, the behavioral and the EEG onset of the seizures can be more readily defined, and clearly originate in the limbic circuit: initial seizure behaviors of immature mice or rats involve arrest of movement, and this freezing is associated with loss of responsiveness to environmental stimuli. The next phase consists of oral automatisms, as typical for limbic human and rodent seizures [47]. Notably, whereas EEG recoding is practically unavailable for the onset of febrile seizures in children, EEG traces from rodents with experimental febrile seizures suggest onset of these seizures in amygdala and hippocampus. Thus, accompanying the Racine stages 0–3 propagation of the behavioral seizures, bipolar electrode recordings from amygdala, hippocampus and cortex showed spike-trains in hippocampus and amygdala with progressively increasing amplitude [20,48,49].

4. Do prolonged febrile seizures cause epilepsy?

The overwhelming evidence from human and animal models suggest that the outcome of short febrile seizures is benign. However, whether prolonged febrile seizures and febrile status epilepticus lead to epilepsy has been more difficult to sort out. Generally, prospective epidemiological evaluations have provided little evidence for epileptogenesis [2,4,8], although those looking at longer time-scales have shown an increasing probability for epilepsy development [50–53]. In contrast, retrospective analyses have linked a history of complex, and particularly of prolonged febrile seizures to temporal lobe epilepsy [9–12] suggesting a potential contribution of febrile seizures to epileptogenesis. The inconsistent nature of these data promoted the use of animal models, to study this issue more directly.

In animal models of long febrile seizures, the seizures are induced in a normal rodent brain (e.g., [17–21,39,40,45,48,54–57]), or in animals that have been subjected to prior insults [58, 59]. Initial studies using an experimental model of prolonged febrile seizures in immature rats without genetic or imposed predisposing factors or insults, employed intermittent observation and EEG recording during daytime [20], and did not demonstrate the onset of spontaneous seizures in rats that had experienced experimental febrile seizures. More recently, nocturnal simultaneous video-EEG recordings demonstrated that these seizures led to limbic (TLE) in ~30% of animals [60]. In addition, inter-ictal epilepti-form discharges were recorded in 15 (88.2%) of these animals exposed to prolonged experimental febrile seizures. Neither the EEG (>400 recorded hours) nor the behavior of normothermic controls and of hyperthermic controls, that experienced hyperthermia but in whom the seizures were prevented, demonstrated any abnormalities [43,60]. These studies support the epileptogenic nature of prolonged febrile seizures [43,60].

5. How might prolonged febrile seizures lead to epilepsy?

The mechanisms by which febrile status epilepticus or prolonged febrile seizures might contribute to the development of temporal lobe epilepsy are not known. The use of animal models might provide some helpful information in this context as well. The prolonged experimental febrile seizures led to transient neuronal injury [19]. Interestingly, the injured

neurons were located in the distribution of the cell loss and gliosis found in humans with mesial temporal sclerosis (MTS). However, the involved neurons did not die, as supported by neuronal counts [19,60,61], and acute apoptosis was not observed even after 60 min-long seizures [19]. Neurogenesis was also not observed after these seizures [56,61–63], and mossy fiber sprouting was minimal [61] and not likely the source of the epileptogenic process.

Several molecular and functional changes took place following the experimental prolonged febrile seizures, and might provide the mechanisms for seizure-evoked hippocampal hyperexcitability [20,64,65]. The full spectrum of the molecular changes induced by the seizures in animal models is under study; however, already established are persistent changes in the expression of specific genes such ion channels and endocannabinoid receptors [55].

Experimental prolonged febrile seizures rapidly led to altered calcium signaling in hippocampal neurons, via the formation of calcium-permeable AMPA channels devoid of the GluR2 subunit [66]. This altered route of calcium entry has been shown to promoted significant number of intracellular cascades, culminating in changes of gene expression [67–69]. One consequence was an alteration the expression of the ions channels governing the properties of I_h, a hyperpolarization-triggered cationic current that contributes to the maintenance of neuronal membrane potential, subthreshold oscillations and dendritic integration [46,65]. This change in I_h promoted frequency-dependent rebound depolarization in response to hyperpolarizing input, which was augmented after the seizures [64,65]. At the molecular level, the changes in I_h appeared to result from persistent altered expression of hyperpolarization-activated cyclic-nucleotide gated (HCN) channels that conduct this current. A reduction of the expression of the HCN1 iso-form was observed, as well as increased formation of HCN1/HCN2 heteromeric channels, which were >200% higher in the CA1 hippocampal region of animals experiencing prolonged febrile seizures compared to controls [49,70]. The relevance of the alterations in HCN channels and I_h to human epileptogenesis is not clear, but HCN1 channel expression was found to be changed also in hippocampi removed from patients with temporal lobe epilepsy and mesial temporal sclerosis, often with a history of early life seizures [71]. This suggests that HCN channel expression is influenced also in human temporal lobe epilepsy. Similarly, it might be speculated that mutations in HCN channel genes which will alter I_h should be discovered in individuals with epilepsy.

A second change provoked by prolonged experimental febrile seizures that promoted hyperexcitability involved altered endocannabinoid signaling. In essence, the seizures increased the number of presynaptic can-nabinoid type 1 receptors, which increased retrograde inhibition of GABA release, promoting hyperexcitability [55]. It is proposed that many other persisting alterations in gene expression will be found after experimental febrile seizures, and perhaps human prolonged febrile seizures. Potentially, common regulatory mechanisms will drive these changes, and the resulting alteration of intrinsic neuronal excitability and the responses of neurons to network input will contribute to the generation of a hyperexcitable state associated with spontaneous seizures.

6. Summary

Seizures provoked by fever are common, and teach us about mechanisms of seizure generation early in life. Whereas simple febrile seizures are benign, the pathophysiology of febrile seizures should be studied so that prolonged seizures and their potential consequences will be better understood. Animal models offer the hope of providing the mechanisms for simple and prolonged febrile seizures, as well as enabling an understanding of the proepileptogenic consequences of prolonged febrile seizures.

Acknowledgments

References

1. Stafstrom, CE. The incidence and prevalence of febrile seizures. In: Baram, TZ.; Shinnar, S., editors. Febrile seizures. San Diego: Academic Press; 2002. p. 1-25.

2. Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors prognostic of unprovoked seizures after febrile convulsions. N Engl J Med 1987;316:493–498. [PubMed: 3807992]

3. Berg AT, Shinnar S, Darefsky AS, Holford TR, Shapiro ED, Salomon ME, et al. Predictors of recurrent febrile seizures: a prospective cohort study. Arch Pediatr Adolesc Med 1997;151:371–378. [PubMed: 9111436]

4. Nelson KB, Ellenberg JH. Prognosis in children with febrile seizures. Pediatrics 1978;61:720–727. [PubMed: 662510]

5. Verity CM, Butler NR, Golding J. Febrile convulsions in a national cohort followed up from birth. II - Medical history and intellectual ability at 5 years of age. Br Med J 1985;290:1311–1315. [PubMed: 3922470]

6. Verity CM, Greenwood R, Golding J. Long-term intellectual and behavioral outcomes of children with febrile convulsions. N Engl J Med 1998;338:1723–1728. [PubMed: 9624192]

7. Berg AT, Shinnar S. Unprovoked seizures in children with febrile seizures: short-term outcome. Neurology 1996;47:562–568. [PubMed: 8757039]

8. Berg AT, Shinnar S. Complex febrile seizures. Epilepsia 1996;37:126–133. [PubMed: 8635422]

9. Cendes F, Andermann F, Dubeau F, Gloor P, Evans A, Jones-Gotman M, et al. Early childhood prolonged febrile convulsions, atrophy and sclerosis of mesial structures, and temporal lobe epilepsy: an MRI volumetric study. Neurology 1993;43:1083–1087. [PubMed: 8170546]

10. French JA, Williamson PD, Thadani VM, Darcey TM, Mattson RH, Spencer SS, et al. Characteristics of medial temporal lobe epilepsy: I. Results of history and physical examination. Ann Neurol 1993;34:774–780. [PubMed: 8250525]

11. Hamati-Haddad A, Abou-Khalil B. Epilepsy diagnosis and localization in patients with antecedent childhood febrile convulsions. Neurology 1998;50:917–922. [PubMed: 9566372]

12. Theodore WH, Bhatia S, Hatta J, Fazilat S, DeCarli C, Bookheimer SY, et al. Hippocampal atrophy, epilepsy duration, and febrile seizures in patients with partial seizures. Neurology 1999;52:132–136. [PubMed: 9921860]

13. Shinnar S, Berg AT, Moshe SL, Shinnar R. How long do new-onset seizures in children last? Ann Neurol 2001;49:659–664. [PubMed: 11357957]

14. Dzhala VI, Talos DM, Sdrulla DA, Brumback AC, Mathews GC, Benke TA, et al. NKCC1 transporter facilitates seizures in the developing brain. Nat Med 2005;11:1205–1213. [PubMed: 16227993]

15. Le Van Quyen M, Khalilov I, Ben-Ari Y. The dark side of high-frequency oscillations in the developing brain. Trends Neurosci 2006;29:419–427. [PubMed: 16793147]

16. Berg AT, Shinnar S, Levy SR, Testa FM. Childhood-onset epilepsy with and without preceding febrile seizures. Neurology 1999;53:1742–1748. [PubMed: 10563622]

17. Holtzman D, Obana K, Olson J. Hyperthermia-induced seizures in the rat pup: a model for febrile convulsions in children. Science 1981;213:1034–1036. [PubMed: 7268407]

18. Morimoto T, Nagao H, Sano N, Takahashi M, Matsuda H. Electroencephalographic study of rat hyperthermic seizures. Epilepsia 1991;32:289–293. [PubMed: 2044491]

19. Toth Z, Yan XX, Haftoglou S, Ribak CE, Baram TZ. Seizure-induced neuronal injury: vulnerability to febrile seizures in an immature rat model. J Neurosci 1998;18:4285–4294. [PubMed: 9592105]

20. Dubé C, Chen K, Eghbal-Ahmadi M, Brunson KL, Soltesz I, Baram TZ. Prolonged febrile seizures in immature rat model enhance hippocampal excitability long-term. Ann Neurol 2000;47:336–344. [PubMed: 10716253]

21. Dubé C, Vezzani A, Behrens M, Bartfai T, Baram TZ. Interleukin-1beta contributes to the generation of experimental febrile seizures. Ann Neurol 2005;57:152–155. [PubMed: 15622539]

22. Wallace RH, Wang DW, Singh R, Scheffer IE, George AL Jr, Phillips HA, et al. Febrile seizures and generalized epilepsy associated with a mutation in the Na+-channel beta1 subunit gene SCN1B. Nat Genet 1998;19:366–370. [PubMed: 9697698]

23. Escayg A, MacDonald BT, Meisler MH, Baulac S, Huberfeld G, An-Gourfinkel I, et al. Mutations of SCN1A, encoding a neuronal sodium channel, in two families with GEFS+2. Nat Genet 2000;24:343–345. [PubMed: 10742094]

24. Harkin LA, Bowser DN, Dibbens LM, Singh R, Phillips F, Wallace RH, et al. Truncation of the GABA(A)-receptor gamma2 subunit in a family with generalized epilepsy with febrile seizures plus. Am J Hum Genet 2002;70:530–536. [PubMed: 11748509]

25. Audenaert D, Schwartz E, Claeys KG, Claes L, Deprez L, Suls A, et al. A novel GABRG2 mutation associated with febrile seizures. Neurology 2006;67:687–690. [PubMed: 16924025]

26. Kang JQ, Shen W, Macdonald RL. Why does fever trigger febrile seizures? GABA$_A$ receptor gamma2 subunit mutations associated with idiopathic generalized epilepsies have temperature-dependent trafficking deficiencies. J Neurosci 2006;26:2590–2597. [PubMed: 16510738]

27. Virta M, Hurme M, Helminen M. Increased frequency of interleukin-1beta (-511) allele 2 in febrile seizures. Pediatr Neurol 2002;26:192–195. [PubMed: 11955925]

28. Tan NC, Mulley JC, Berkovic SF. Genetic association studies in epilepsy: "the truth is out there". Epilepsia 2004;45:1429–1442. [PubMed: 15509244]

29. Moser E, Mathiesen I, Andersen P. Association between brain temperature and dentate field potentials in exploring and swimming rats. Science 1993;259:1324–1326. [PubMed: 8446900]

30. Shibasaki K, Suzuki M, Mizuno A, Tominaga M. Effects of body temperature on neural activity in the hippocampus: regulation of resting membrane potentials by transient receptor potential vanilloid 4. J Neurosci 2007;27:1566–1575. [PubMed: 17301165]

31. Fukuda M, Morimoto T, Nagao H, Kida K. Clinical study of epilepsy with severe febrile seizures and seizures induced by hot water bath. Brain Dev 1997;19:212–216. [PubMed: 9134194]

32. Cartmell T, Luheshi GN, Rothwell NJ. Brain sites of action of endogenous interleukin-1 in the febrile response to localized inflammation in the rat. J Physiol 1999;518:585–594. [PubMed: 10381603]

33. Alheim K, Bartfai T. The interleukin-1 system: receptors, ligands, and ICE in the brain and their involvement in the fever response. Ann NY Acad Sci 1998;840:51–58. [PubMed: 9629236]

34. Takao T, Tracey DE, Mitchell WM, De Souza EB. Interleukin-1 receptors in mouse brain: Characterization and neuronal localization. Endocrinology 1990;127:3070–3078. [PubMed: 2147409]

35. Ban E, Milon G, Prudhomme N, Fillion G, Haour F. Receptors for interleukin-1 (alpha and beta) in mouse brain: mapping and neuronal localization in hippocampus. Neuroscience 1991;43:21–30. [PubMed: 1833666]

36. Cartmell T, Southgate T, Rees GS, Castro MG, Loweinstein PR, Luheshi GN. Interleukin-1 mediates a rapid inflammatory response after injection of adenoviral vectors into the brain. J Neurosci 1999;19:1517–1523. [PubMed: 9952427]

37. Gatti, S.; Vezzani, A.; Bartfai, T. Mechanisms of fever and febrile seizures: putative role of interleukin-1 system. In: Baram, TZ.; Shinnar, S., editors. Febrile seizures. San Diego: Academic Press; 2002. p. 169-188.

38. Vezzani A, Granata T. Brain inflammation in epilepsy: experimental and clinical evidence. Epilepsia 2005;46:1724–1743. [PubMed: 16302852]

39. Heida JG, Boissé L, Pittman QJ. Lipopolysaccharide-induced febrile convulsions in the rat: short-term sequelae. Epilepsia 2004;45:1317–1329. [PubMed: 15509232]

40. Heida JG, Pittman QJ. Causal links between brain cytokines and experimental febrile convulsions in the rat. Epilepsia 2005;46:1906–1913. [PubMed: 16393156]

41. Barone SR, Kaplan MH, Krilov LR. Human herpesvirus-6 infection in children with first febrile seizures. J Pediatr 1995;127:95–97. [PubMed: 7608818]

42. Zerr DM, Meier AS, Selke SS, Frenkel LM, Huang ML, Wald A, et al. A population-based study of primary human herpesvirus 6 infection. N Engl J Med 2005;352:768–776. [PubMed: 15728809]

43. Dubé CM, Brewster AL, Richichi C, Zha Q, Baram TZ. Fever, febrile seizures and epilepsy. Trends Neurosci 2007;30:490–496. [PubMed: 17897728]

44. Aram JA, Lodge D. Epileptiform activity induced by alkalosis in rat neocortical slices: block by antagonists of N-methyl-D-aspartate. Neurosci Lett 1987;83:345–350. [PubMed: 2894627]

45. Balestrino M, Somjen CG. Concentration of carbon dioxide, interstitial pH and synaptic transmission in hippocampal formation of the rat. J Physiol 1988;396:247–266. [PubMed: 2842490]

46. Schuchmann S, Schmitz D, Rivera C, Vanhatalo S, Salmen B, Mackie K, et al. Experimental febrile seizures are precipitated by a hyperthermia-induced respiratory alkalosis. Nat Med 2006;12:817–823. [PubMed: 16819552]

47. Racine RJ. Modification of seizure activity by electrical stimulation. II. Motor seizure. Electroencephalogr Clin Neurophysiol 1972;32:281–294. [PubMed: 4110397]

48. Baram TZ, Gerth A, Schultz L. Febrile seizures: an appropriate-aged model suitable for long-term studies. Dev Brain Res 1997;98:265–270. [PubMed: 9051269]

49. Brewster A, Bender RA, Chen Y, Dubé C, Eghbal-Ahmadi M, Baram TZ. Developmental febrile seizures modulate hippocampal gene expression of hyperpolarization-activated channels in an isoform- and cell-specific manner. J Neurosci 2002;22:4591–4599. [PubMed: 12040066]

50. Annegers JF, Hauser WA, Elveback LR, Kurland LT. The risk of epilepsy following febrile convulsions. Neurology 1979;29:297–303. [PubMed: 571973]

51. Verity CM, Ross EM, Golding J. Outcome of childhood status epilepticus and lengthy febrile convulsions: findings of national cohort study. Br Med J 1993;307:225–228. [PubMed: 8369681]

52. Raspall-Chaure M, Chin RF, Neville BG, Scott RC. Outcome of paediatric convulsive status epilepticus: a systematic review. Lancet Neurol 2006;5:769–779. [PubMed: 16914405]

53. Provenzale JM, Barboriak DP, VanLandingham K, MacFall J, Delong D, Lewis DV. Hippocampal MRI signal hyperintensity after febrile status epilepticus is predictive of subsequent mesial temporal sclerosis. Am J Roentgenol 2008;190:976–983. [PubMed: 18356445]

54. Chang YC, Huang AM, Kuo YM, Wang ST, Chang YY, Huang CC. Febrile seizures impair memory and cAMP response-element binding protein activation. Ann Neurol 2003;54:706–718. [PubMed: 14681880]

55. Chen K, Ratzliff A, Hilgenberg L, Gulyas A, Freund TF, Smith M, et al. Long-term plasticity of endocannabinoid signaling induced by developmental febrile seizures. Neuron 2003;14(39):599–611. [PubMed: 12925275]

56. Lemmens EM, Lubbers T, Schijns OE, Beuls EA, Hoogland G. Gender differences in febrile seizure-induced proliferation and survival in the rat dentate gyrus. Epilepsia 2005;46:1603–1612. [PubMed: 16190931]

57. Kamal A, Notenboom RG, de Graan PN, Ramakers GM. Persistent changes in action potential broadening and the slow afterhyperpolarization in rat CA1 pyramidal cells after febrile seizures. Eur J Neurosci 2006;23:2230–2234. [PubMed: 16630069]

58. Germano IM, Zhang YF, Sperber EF, Moshé SL. Neuronal migration disorders increase susceptibility to hyperthermia-induced seizures in developing rats. Epilepsia 1996;37:902–910. [PubMed: 8814104]

59. Scantlebury MH, Gibbs SA, Foadjo B, Lema P, Psarropoulou C, Carmant L. Febrile seizures in the predisposed brain: a new model of temporal lobe epilepsy. Ann Neurol 2005;58:41–49. [PubMed: 15940665]

60. Dubé C, Richichi C, Bender RA, Chung G, Litt B, Baram TZ. Temporal lobe epilepsy after experimental prolonged febrile seizures: prospective analysis. Brain 2006;129:911–922. [PubMed: 16446281]

61. Bender RA, Dubé C, Gonzalez-Vega R, Mina EW, Baram TZ. Mossy fiber plasticity and enhanced hippocampal excitability, without hippocampal cell loss or altered neurogenesis, in an animal model of prolonged febrile seizures. Hippocampus 2003;13:399–412. [PubMed: 12722980]

62. Jiang W, Duong TM, de Lanerolle NC. The neuropathology of hyperthermic seizures in the rat. Epilepsia 1999;40:5–19. [PubMed: 9924896]

63. Baram TZ, Eghbal-Ahmadi M, Bender RA. Is neuronal death required for seizure-induced epileptogenesis in the immature brain? Prog Brain Res 2002;135:365–375. [PubMed: 12143355]

64. Chen K, Baram TZ, Soltesz I. Febrile seizures in the developing brain result in persistent modification of neuronal excitability in limbic circuits. Nat Med 1999;5:888–894. [PubMed: 10426311]

65. Chen K, Aradi I, Thon N, Eghbal-Ahmadi M, Baram TZ, Soltesz I. Persistently modified h-channels after complex febrile seizures convert the seizure-induced enhancement of inhibition to hyper-excitability. Nat Med 2001;7:331–337. [PubMed: 11231632]

66. Richichi C, Brewster AL, Bender RA, Simeone TA, Zha Q, Yin HZ, et al. Mechanisms of seizure-induced 'transcriptional channelopathy' of hyperpolarization-activated cyclic nucleotide gated (HCN) channels. Neurobiol Dis 2008;29:297–305. [PubMed: 17964174]

67. Pellegrini-Giampietro DE, Gorter JA, Bennett MV, Zukin RS. The GluR2 (GluR-B) hypothesis: Ca (2+)-permeable AMPA receptors in neurological disorders. Trends Neurosci 1997;20:464–470. [PubMed: 9347614]

68. Sanchez RM, Dai W, Levada RE, Lippman JJ, Jensen FE. AMPA/kainate receptor-mediated downregulation of GABAergic synaptic transmission by calcineurin after seizures in the developing rat brain. J Neurosci 2005;25:3442–3451. [PubMed: 15800199]

69. Isaac JT, Ashby M, McBain CJ. The role of the GluR2 subunit in AMPA receptor function and synaptic plasticity. Neuron 2007;54:859–871. [PubMed: 17582328]

70. Brewster AL, Bernard JA, Gall CM, Baram TZ. Formation of heteromeric hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in the hippocampus is regulated by developmental seizures. Neurobiol Dis 2005;19:200–207. [PubMed: 15837575]

71. Bender RA, Soleymani SV, Brewster AL, Nguyen ST, Beck H, Mathern GW, et al. Enhanced expression of a specific hyperpolarization-activated cyclic nucleotide-gated cation channel (HCN) in surviving dentate gyrus granule cells of human and experimental epileptic hippocampus. J Neurosci 2003;23:6826–6836. [PubMed: 12890777]

72. Kim, JA.; Gibson, HE.; Kauer, JA.; Connors, BW. TRPV1 channels enhance susceptibility to febrile seizures. Annual meeting of the Society for Neuroscience; November 15–19; Washington DC. 2008. Abstr Soc Neurosci # 628.1

73. Tütüncüoğlu S, Kütükçü ler N, Kepe L, Coker C, Berdeli A, Tekgül H. Proinflammatory cytokines, prostaglandins and zinc in febrile convulsions. Pediatr Int 2001;43:235–239. [PubMed: 11380915]

74. Haspolat S, Mihçi E, Coşkun M, Gümü slü S, Ozben T, Yeğin O. Interleukin-1beta, tumor necrosis factor-alpha, and nitrite levels in febrile seizures. J Child Neurol 2002;17:749–751. [PubMed: 12546429]

75. Lahat E, Livne M, Barr J, Katz Y. Interleukin-1beta levels in serum and cerebrospinal fluid of children with febrile seizures. Pediatr Neurol 1997;17:34–36. [PubMed: 9308973]

76. Ichiyama T, Nishikawa M, Yoshitomi T, Hayashi T, Furukawa S. Tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6 in cerebrospinal fluid from children with prolonged febrile seizures. Comparison with acute encephalitis/encephalopathy. Neurology 1998;50:407–411. [PubMed: 9484363]

77. Morimoto T, Fukuda M, Aibara Y, Nagao H, Kida K. The influence of blood gas changes on hyperthermia-induced seizures in developing rats. Dev Brain Res 1996;92:77–80. [PubMed: 8861725]

78. Berg AT. Are febrile seizures provoked by a rapid rise in temperature? Am J Dis Child 1993;147:1101–1103. [PubMed: 8213683]

Table 1

Mechanisms of febrile seizures generation.

Mechanisms	Animal models	Humans
↑ Brain temperature	Activation of temperature-sensitive channels including transient receptor potential vanilloid [30,72] Modulation of amplitude and kinetics of ionic currents [29]	Hyperthermia induced by hot bath and anticholinergic medication [31]
Fever mediators: interleukin-1β	↑ Seizure threshold temperature in IL1RI deficient mice [21] ↑ Hippocampal IL-1β levels at FS onset [40] Exogenous IL1-RA inhibits FS [40]	↑ Frequency of allele promoting IL-1β production in children with FS [27] CSF: ↑ IL-1β in children with FS [73,74] However, no ↑ IL-1β in CSF in children with FS [75,76]
Genetic factors	Seizure threshold temperature is strain dependent in mice [21] Mutation in GABA$_A$ receptors γ2 subunits [26]	Mutation in GABA$_A$ receptors γ2 subunits and sodium channels (SCN1A and B) found in individuals with GEFP+ [22–25]
Hyperthermia-induced hyperventilation and alkalosis	Alkalosis may promote FS [46,77]	Controversial [78]