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Fever, febrile seizures and epilepsy

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Seizures induced by fever (febrile seizures) are the most common type of pathological brain activity in infants and children. These febrile seizures and their potential contribution to the mechanisms of limbic (temporal lobe) epilepsy have been a topic of major clinical and scientific interest. Key questions include the mechanisms by which fever generates seizures, the effects of long febrile seizures on neuronal function and the potential contribution of these seizures to epilepsy. This review builds on recent advances derived from animal models and summarizes our current knowledge of the mechanisms underlying febrile seizures and of changes in neuronal gene expression and function that facilitate the enduring effects of prolonged febrile seizures on neuronal and network excitability. The review also discusses the relevance of these findings to the general mechanisms of epileptogenesis during development and points out gaps in our knowledge, including the relationship of animal models to human febrile seizures and epilepsy.

Introduction

Fever provokes seizures in one out of 20–50 children, so that these convulsions, termed 'ebrile seizures', are the most common form of pathological brain activity during development [1,2]. In addition, although there is little evidence for an enduring adverse impact of short febrile seizures on the developing brain [1], prolonged or focal febrile seizures (see Glossary) have been associated statistically with the development of intractable epilepsy that involves the limbic circuit (temporal lobe epilepsy; reviewed in [3]). Not surprisingly, these seizures, their underlying mechanisms and their consequences have been a focus of interest for pediatricians and for physicians who treat individuals with epilepsy. In addition, as eloquent examples of perturbed neuronal circuit activity early in life and of activity-dependent plasticity, these seizures have attracted the attention of developmental and systems neurobiologists. To facilitate investigation of these seizures, several animal models of prolonged febrile seizures have been developed (e.g. [4–11]). Over recent years, these models have led to fundamental discoveries about the mechanisms of these seizures, their effects on neuronal excitability [12–18] and their relationship to epilepsy (epileptogenesis, see Box 1). These recent discoveries and the many remaining gaps in our knowledge are the focus of this review.

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Mechanisms by which fever leads to 'febrile' seizures

Genetic susceptibility to febrile seizures

Febrile seizures occur sporadically and also run in families, so that the contribution of genetic background to their onset has been an active topic of discussion [19]. In immature rodents, hyperthermia provokes seizures in virtually all subjects, suggesting that genetic susceptibility is not a prerequisite for their generation [4,5,7,13]. However, mouse strains differ in their seizure-threshold temperature (a measure of susceptibility [20]), suggesting the involvement of genotype in these seizures. In addition, specific mutations of several ion channels that predispose to febrile seizures have been described in humans [21–24] and rodent models [25]. Among these, mutations of sodium [21,22] and chloride ($GABA_A$ [gamma aminobutyric acid A] receptor) [23–25] channels have been prominent. Other single gene mutations might also render individuals more

Glossary

Complex febrile seizures: those that last longer than 10–15 minutes or that are focal (arising from a specific brain region and manifesting as movement of one limb or side of the body).
Epilepsy: occurrence of unprovoked (spontaneous) seizures, typically unpredictably.
Epileptogenesis: the process of the transformation of a 'normal' neuronal network into one capable of generating unprovoked seizures.
Febrile seizures: seizures that accompany fever, typically occurring at the onset of the fever. These are found in infants and children (3–6 months to 5–6 years), with peak incidence at approximately 18 months of age.
Febrile status epilepticus: an arbitrary term denoting prolonged febrile seizures lasting more than 30 minutes.
Focal seizures: seizures involving only a portion of the brain. This is apparent from their behavioral manifestations and/or EEG correlates.
Limbic seizures: seizures involving the limbic circuit that includes amygdala, hippocampus and inter-related cortices. Behavioral features typically include freezing, mouth automatisms (i.e. lip smacking, chewing) and altered consciousness.
Mesial temporal sclerosis: loss of neurons and gliosis in specific regions of the hippocampal formation that is found in a significant portion of individuals with temporal-lobe epilepsy.
Prospective studies: subjects are identified at or close to the time of the event, information is collected contemporaneously in an organized manner and the outcomes are determined. Particularly when population-based, these studies avoid selection artifacts and recall bias. Conversely, they might miss small-probability associations, are long and require large numbers of subjects.
Retrospective studies: individuals or cases are identified after the fact (or with a known outcome, such as epilepsy) and evaluated retroactively. These studies can identify associations in relatively small populations but are open to ascertainment and recall biases and might assess selected (e.g., more severely affected) populations that do not reflect a general principle.
Seizure: a paroxysm of abnormal activity of neuronal populations. This typically has to last longer that 3 seconds, be detectable using electrophysiological measures (EEG) and be associated with a change in behavior.
Simple febrile seizures: short (<10 minutes, usually <5 minutes), without focal features.
Temporal lobe epilepsy: epilepsy arising in and engaging primarily the limbic circuit, located in humans in the temporal lobe of the brain.

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Box 1. Fever, febrile seizures and epilepsy: take-home messages

- Febrile seizures are an excellent model of abnormal network activity during development because they do not occur later in life. In addition, they provide biologically relevant examples of activity-dependent, enduring plasticity [14–16,53,56]. The additional importance of these seizures derives from the statistical association of prolonged febrile seizures to human temporal-lobe epilepsy [3]. Animal models of these seizures [4,5,7,11,13,17] offer opportunities to investigate potential causal relationships of these seizures and human epilepsy.
- Studies of the evolution of epilepsy after experimental prolonged febrile seizures suggest that epileptogenesis early in postnatal life might not require cell death [17,52,53]. Rather, enduring functional changes in neuronal and network behavior might provoke episodic hyper-excitability and seizures. These changes are governed by enduring alteration of expression, post-translational modification and function of molecules that govern neuronal excitability (e.g. ion channels and receptors) [12,14,16,52,54–56,59,60]. Among the many changes described (Table 1), altered I_h and altered endocannabinoid signaling have been characterized to date and promote transformation of the hippocampal network into one where seizures can be triggered easily.
- The role of genetic factors in both the generation of febrile seizures and their consequences is an important area for investigation. Mutations of ion-channel genes predispose to febrile seizures and influence their relationship to epilepsy [21–24]. The involvement of HCN channels and cannabinoid receptors in the epileptogenic process that follows long experimental febrile seizures suggests that certain mutations in these genes should be epileptogenic.

susceptible to febrile seizures (see below) and multigene interactions might contribute to the occurrence of these seizures in a more complex and subtle way. In summary, the contribution of the gene–environment interaction to the generation of febrile seizures and to their potential causal relationship to epilepsy [26] is a topic of active investigation. The availability of increasingly sophisticated experimental tools predicts that major breakthroughs in our understanding of the issues involved should emerge in the next few years.

Does fever generate seizures by elevating brain temperature?

Temperature influences numerous cellular processes, including the electrical activity of neurons [27]. The functions of several neuronal ion channels are dependent markedly on temperature in the physiological and fever ranges, approximately 36–42 °C (e.g. TRPV4 [transient receptor potential vanilloid 4] [28]), and temperature also modulates the amplitude and kinetics of major ionic currents [29]. These facts suggest that an increase in the temperature of neuronal tissue could enhance the rate, magnitude or synchrony of neuronal firing, leading to seizures; this notion is supported by the fact that, in children, hyperthermia induced by hot baths or anticholinergic medications might also provoke seizures [30]. Measuring brain temperature is not feasible in children with fever; however, direct measurements of intradural temperatures and their correlation with core-body values under normal conditions and during hyperthermia have been carried out in rodent models [31], confirming that, during hyperthermia, brain temperature rises immediately preceding the onset of seizures. However, whether increased temperature *per se* suffices to generate electrophysiological and behavioral seizures has remained unclear. Heating brain slices in a dish altered the electrophysiological properties of the hippocampal network but did not provoke clear seizure-like events [32]. By contrast, hyperthermia has been shown recently to alter the activity of certain mutated ion channels, enhancing circuit excitability [25]. Thus, further work is required to determine the direct role of increased temperature in the generation of febrile seizures.

Fever mediators contribute to the generation of febrile seizures

Fever involves the release of cytokines and other inflammatory mediators in the body and within the brain itself [33,34]. Certain cytokines, and specifically interleukin (IL)-1β, enhance neuronal excitability, in part by augmenting glutamate-receptor function [35]. *In vivo*, these actions of IL-1β enhance the actions of seizure-provoking agents [35]. The possibility that brain hyperthermia might elicit rapid release of endogenous IL-1β [34], which, in turn, contributes to the generation of seizures, was supported by the markedly increased temperature required to induce experimental febrile seizures in mice lacking the IL-1β receptor [20]. Interestingly, mutations in the *IL-1β* gene promoter that result in increased production of the cytokine have been reported in individuals with febrile seizures [36], although the significance of this finding has been debated [37]. Thus, available data support a significant role for temperature-induced release of endogenous IL-1β in the mechanisms by which hyperthermia – and fever – generates seizures in rodents and humans [9,38]. However, other factors that characterize selectively specific stages of brain development probably contribute in a major way to the age specificity of human and experimental febrile seizures [39,40], as discussed below.

The possibility that fever of specific infectious etiologies might contribute to the generation of human febrile seizures is intriguing in this context: a disproportionate number of febrile seizures have been associated with infection with HHV6 (human herpes virus 6) in some [41] but not all studies [42]. This suggests that mechanisms specific to this virus, including perhaps a unique profile of cytokine induction, might augment neuronal excitability selectively and thus provoke seizures preferentially.

Hyperthermia-induced hyperventilation and alkalosis

Alkalosis of the neuronal environment promotes excitability by several mechanisms [43,44]. The notion that alkalosis might be a key determinant of experimental and human febrile seizures has been proposed [11,45]. In a novel model of febrile seizures, immature rats placed in a heated chamber developed hyperventilation, alkalosis and eventual seizures (Figure 1). In an elegant series of experiments, the alkalosis governed the onset of the seizures; these developed with a latency of 30 min. In other models of febrile seizures, the delay from hyperthermia to seizure-onset was shorter [6,8,46] and did not seem to evoke hyperventilation ([46], see Figure 1 for a comparative analysis of the models). Whether alkalosis is instrumental in human febrile seizures

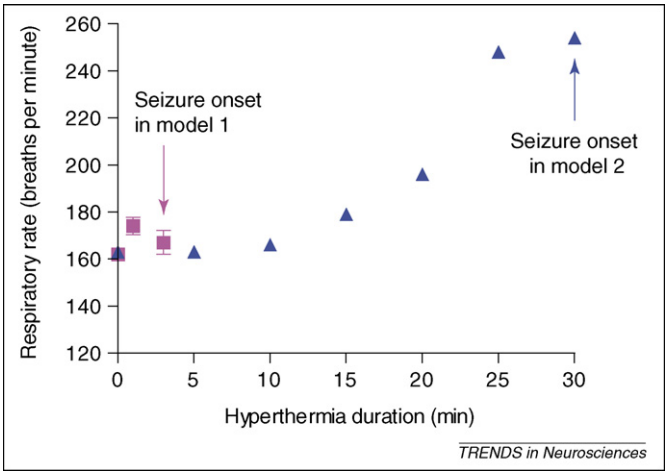

Figure 1. Comparison of latency to seizure onset and of hyperventilation in two established rodent models of experimental febrile seizures [11,13,46]. In the first model (shown in fuchsia), which uses a hair-dryer to emit a warmed stream of air, seizures commence within 2.9 ± 0.1 min after the initiation of the heating procedure. Increase of temperature is rapid, rising from 33.4 ± 0.16 °C to 40.74 ± 0.13 °C (the seizure-threshold temperature) in 2.9 min, with little change in respiratory rates: 161.8 ± 2.6 (n = 12) at baseline and 166.9 ± 4.9 during the minute preceding seizure onset [p = 0.37 versus baseline (values in the graph are shown as mean ± SEM; derived from [31,46]). In the second model, in which rats are placed in a heated chamber, seizures commence approximately 31 min after initiation of the heating procedure, when body temperature rises from 33.4 ± 0.9 to 41.8 ± 0.7 °C. Respiratory rate begins to increase significantly approximately 15 min into the procedure and the increased respiratory rate over approximately 15 min before the onset of the seizures promotes brain alkalosis (derived from [11]).

remains unresolved [47]: the presence of alkalosis already at the onset of febrile seizures will support its contribution to their generation. This will require arterial pH measurements at the onset of febrile seizures, yet these seizures rarely commence in settings permitting this analysis.

Effects of prolonged febrile seizures on neuronal structure and function

Do prolonged febrile seizures lead to epilepsy? Clinical issues and experimental approaches

In prospective human studies, short or simple febrile seizures do not seem to have significant consequences on neuronal function (measured by cognitive tests) or on the probability of epilepsy development [1], although, in very young children, subtle deficits in hippocampus-dependent learning functions might occur [48]. However, the epileptogenic potential of prolonged and/or focal febrile seizures has remained unclear. Prospective studies find a small but significant increased risk for epilepsy and a history of long febrile seizures in individuals who already have temporal lobe epilepsy is common (approximately 30–70%; reviewed in [3]). Human studies are correlative and cannot distinguish between a causal effect of long febrile seizures on epilepsy versus the possibility that pre-existing factors (genetic or acquired) might incite febrile seizures and epilepsy independently or influence the probability that these seizures lead to limbic epilepsy.

Animal models of prolonged febrile seizures have addressed these issues [8,15,17]. Studies of rats subjected to experimental prolonged febrile seizures at the stage of hippocampal development that corresponds to that of human infants [49] followed by chronic video-EEG monitoring demonstrated that a minority of these animals developed limbic epilepsy [17]. Epilepsy or abnormal EEG were absent in controls and in rats that experienced early-life hyperthermia without seizures, supporting the notion that the epilepsy was a direct consequence of the inciting 'febrile' seizures. Thus, at least in animal models, prolonged 'febrile' seizures can evoke epilepsy, providing a tool for elucidating the responsible mechanisms, for discovering biomarkers for epileptogenesis and for defining windows of opportunity for therapeutic and/or preventive interventions. Clearly, whether epileptogenic processes occurring in the immature rodent brain are analogous directly to those in children remains largely unknown. Parallel human and animal studies, including imaging and molecular analyses, should delineate similarities and divergences among children and immature rats. Ultimately, this issue will be resolved by interventional studies using molecular targets discovered in the animal model and by aiming to prevent human epileptogenesis.

Experimental prolonged febrile seizure-induced epilepsy provides clues to the puzzle of early-life epileptogenesis

Although the relevance of experimental long febrile seizures to human disease is not elucidated fully, the occurrence of spontaneous seizures (epilepsy) after these seizures provides a window into the age-specific processes underlying epileptogenesis during the developmental period. For example, a classical mechanism of epileptogenesis in the mature hippocampus involves loss of vulnerable populations of neurons and reorganization of the remaining circuit [50]. However, significant neuronal loss was not found following single or repeated episodes of experimental febrile seizures [7,15,51], including in rats that became epileptic [17]. This is consistent with the demonstration of epileptogenesis without significant 'damage' in other developmental models [52,53] and introduces several concepts regarding early-life epileptogenesis in general. First, the epileptogenic process initiated during development might depend on altered neuronal function, rather than neuronal demise (as discussed later). Second, in human temporal lobe epilepsy with a history of early-life febrile seizures, in which cell loss [mesial temporal sclerosis (MTS)] is often found, the epilepsy might precede – and provoke – MTS.

Changes evoked by prolonged experimental febrile seizures promote neuronal excitability and seizures

As mentioned earlier, experimental febrile seizures as well as developmental lithium-pilocarpine [53] or tetanus toxin [52] seizures share a common general mechanism for enhancing hippocampal network excitability and promoting epilepsy. This process involves enduring changes at the molecular and functional levels, such as alterations in neurotransmitter receptors [54,55] or voltage-gated ion channels [14,56]. A wide spectrum of molecular changes has been described after experimental febrile seizures (Table 1); however, the contribution of a given alteration to neuronal excitability and, specifically, to the generation of episodic seizures has been elucidated only for two. These are discussed in the following paragraphs.

Table 1. Changes occurring after experimental or human febrile seizures and their relevance to human epilepsy

Change	Animal models	Humans	Significance for epileptogenesis
Structural			
Neuronal death	None in hippocampus [7,17,51] None [15] None for short FS; neuronal loss after long (median 4 h) seizures [8]	Unknown MRI changes, see below	Epileptogenesis found without cell death in rat model [17]
Neuronal injury	Transient cytoskeletal changes [7] Basophilia in hippocampus [68]	MRI signal change consistent with edema [69–71]	Not clear
Sprouting of mossy fibers	Minimal, delayed (3 months) [51] Modest, at 6 months [8] None at 2 months [15]	Unknown Found in hippocampi of TLE patients with history of FS [3,50]	Not always found in human TLE with FS history; absent in FS-evoked epilepsy in models
Neurogenesis	None at 3, 7, or 28 days [51] None at a week; increased at 7 weeks [10]	Unknown Granule cell dispersion in TLE [72]	Not clear
MRI changes after prolonged febrile seizures	↑ T2 signal in hippocampus and other limbic structures at a day to 4 weeks [73]	↑ hippocampal T2 signal within days [69] Transient ↑ hippocampal T2 and volume at 2 days [70,71] ↑ hippocampal volume, and DWI intensity within 5 days [74]	Potential biomarker
Molecular			
Interleukin-1β (IL-1β)	↑ seizure threshold temperature in IL-1RI deficient mice [20] ↑ hippocampal IL-1β levels within hours [9]	↑ frequency of allele promoting IL-1β production in children with FS [36] CSF: ↑ IL-1β in children with FS [75,76] ↑ frequency of allele promoting IL-1β synthesis in TLE [77]	Not clear
Other cytokines Interleukin 6	↑ experimental febrile seizure latency [78]	CSF: ↑ IL-6 in children with FS [36,75]	Not required
Neuropeptide Y	↑ hippocampal NPY hours after FS [31]	Unknown	Unknown
NMDA receptors	↓ NR2A-mediated $ERK_{1/2}$ phosphorylation after learning tasks at a month after 9 'FS' [79]	Unknown	Unknown
AMPA receptors	Transient ↓ of GluR2 at 1 day	Unknown	Unknown
HCN channels	↓ *HCN1* expression ↑ heteromeric HCN1/HCN2, altered I_h [56,60]	Increased hippocampal *HCN1* expression in TLE with MTS [61]	Defined in model, not clear in human
CB1 receptors	Enduring ↑interneuronal *CB1* receptor expression [16,66]	Unknown	Reduces inhibition in model; in human?
Fos	Transient ↑ in hippocampus [80] Transient ↑ in limbic and cortical areas [81]	Unknown	Unknown
CREB	↓ CREB phosphorylation after learning tasks at 1 month after 9 experimental FS [15]	Unknown	Unknown
Functional			
GABAergic neurotransmission	↑ PKA dependent presynaptic GABAergic inhibition in CA1 at 1 week [12] Mutations in $GABA_A$ receptors γ2 subunits promote experimental FS [25] ↓$GABA_B$ receptor inhibition, hippocampus [82]	Mutations in $GABA_A$ receptors γ2 found in individuals with FS+ (GEFS +) [23,24] Low CSF GABA in FS children [83]	Not clear
I_h	Altered properties (see text) [14,18]	Unknown	Unknown
Endocannabinoid signaling	Potentiated suppression of inhibition (see text) [16,66]	Unknown	Unknown
Seizure susceptibility	No change (to PTZ) at 2 months [15] Enduring ↑susceptibility to kainic acid and tetanic stimulation *in vitro* [13] Spontaneous seizures after 'latent period' [17]	↑ risk of unprovoked seizures [84]	Denotes causality in model, supports it in human

The contribution of altered I_h and HCN channel expression to neuronal excitability and seizures

Following experimental prolonged febrile seizures, the properties of I_h, a hyperpolarization-triggered cationic current that contributes to the maintenance of neuronal membrane potential, sub-threshold oscillations and dendritic integration [57–59], were altered in hippocampal pyramidal cells [11,14]. The altered properties of I_h led to the increased probability of frequency-dependent rebound depolarization in response to hyperpolarizing input [14] (which itself was augmented after the seizures [12]). Interestingly, this increased firing probability occurred only in response to hyperpolarizing pulses at a limited frequency range, a fact that helps explain the

absence of continuous seizures but the generation of sporadic ones (epilepsy). The abnormal firing of a neuron with altered I_h, a firing that might incite a seizure, would only occur under specific circumstances, i.e., when the neuron receives inhibitory input that is within the vulnerable frequency range. At the molecular level, these changes were a result of enduring (for months) changes in the expression of hyperpolarization-activated cyclic-nucleotide-gated (HCN) channels that conduct this current and perhaps also of increased formation of HCN1/HCN2 heteromeric channels [56,60]. HCN channels are encoded by four genes; *HCN1* and *HCN2* are expressed the most abundantly in mature hippocampus. Each functional HCN channel consists of four subunits assembled as homomeric or heteromeric tetramers and the composition and relative abundance of the HCN-channel isoform within a given neuron govern the properties of cellular I_h (reviewed in [58,59]). The relevance of the alterations in HCN channels and I_h to human epileptogenesis remains to be defined fully. Altered HCN1 channel expression was found in hippocampi from a subset of humans with temporal-lobe epilepsy and MTS [61]. However, whether mutations in *HCN* channel genes that alter I_h cause human epilepsy remains unknown.

The contribution of cannabinoid receptors and augmented depolarization-induced suppression of inhibition to network excitability and seizures

Prolonged experimental febrile seizures also promoted network hyperexcitability by leading to a selective reduction of inhibition onto hippocampal principal cells. This was a result of enduring augmentation of depolarization-induced suppression of inhibition (DSI) [16]. DSI is mediated by cannabinoid receptors (CB1) residing in presynaptic neurons [62–65]: in essence, DSI occurs when postsynaptic depolarization elicits the local release of endocannabinoids. When these bind CB1 receptors within presynaptic GABAergic interneurons, GABA release is blocked from these terminals [64], reducing inhibitory input from these interneurons to pyramidal cells. The numbers of pre-synaptic, interneuronal CB1 receptors increased after experimental febrile seizures, which led to larger DSI [11,16], thus selectively reducing inhibition in the involved hippocampal circuit. The initiation of DSI requires depolarization of principal cells, so that its destabilizing effects on the network should be episodic, promoting epilepsy rather than continuous seizures [66]. Functional CB1 receptors exist in human hippocampal formation [67]; whether their expression or function is altered in temporal-lobe epilepsy has not been reported. CB1 receptors also reside in glutamatergic neurons, where they might promote neuroprotection [65]. Therefore, the potential contributions of human *CB1* gene mutations to epilepsy are difficult to predict.

Obviously, the two examples discussed here are the 'tip of the iceberg'. Gene-array and functional studies (Table 1) indicate that prolonged experimental febrile seizures lead to broad changes in the gene-expression programs of numerous molecules (ion channels, receptors, transcription factors) that govern neuronal excitability and network responses. Further work is required to examine these changes and discern whether they contribute to hyperexcitability, are compensatory or are merely epiphenomena, as well as to determine their relevance to febrile seizures and epileptogenesis in children.

Summary

Studying febrile seizures, their mechanisms and their consequences has benefited from animal models, leading to novel discoveries. However, significant gaps in our knowledge remain, including the role of genetic susceptibility in the occurrence of febrile seizures and the enduring effects of these seizures on neuronal function. Fever might promote neuronal excitability through one or a combination of several mechanisms, including hyperthermia *per se*, inflammatory cytokines and alkalosis, perhaps in the setting of genetic susceptibility. Although short febrile seizures do not seem to elicit long-lasting changes in neuronal function, prolonged experimental febrile seizures might lead to limbic epilepsy. This occurs without cell death, suggesting that, during development, the epileptogenic process does not require neuronal loss. The mechanisms mediating early-life epileptogenesis remain unknown but might involve enduring changes in the expression of key molecules that govern neuronal network function. The relevance of the concepts and mechanisms derived from animal models of prolonged febrile seizures to febrile seizures and epileptogenesis in children remains largely unknown. Parallel human and animal studies, including imaging and molecular analyses, should delineate similarities and divergences among children and immature rats. Ultimately, this issue will be resolved by interventional studies using molecular targets discovered in the animal model and aiming to prevent epileptogenesis in susceptible children who have experienced prolonged febrile seizures.

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