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REVIEW

Generation of Febrile Seizures and Subsequent Epileptogenesis

Bo Feng[1] · **Zhong Chen**[1]

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Abstract Febrile seizures (FSs) occur commonly in children aged from 6 months to 5 years. Complex (repetitive or prolonged) FSs, but not simple FSs, can lead to permanent brain modification. Human infants and immature rodents that have experienced complex FSs have a high risk of subsequent temporal lobe epilepsy. However, the causes of FSs and the mechanisms underlying the subsequent epileptogenesis remain unknown. Here, we mainly focus on two major questions concerning FSs: how fever triggers seizures, and how epileptogenesis occurs after FSs. The risk factors responsible for the occurrence of FSs and the epileptogenesis after prolonged FSs are thoroughly summarized and discussed. An understanding of these factors can provide potential therapeutic targets for the prevention of FSs and also yield biomarkers for identifying patients at risk of epileptogenesis following FSs.

Keywords Febrile seizures · Epilepsy · Epileptogenesis

Introduction

Febrile seizures (FSs) are the most common type of convulsive event that take place in early childhood [1]. About 2% to 4% of children experience at least one convulsion along with fever before the fifth year in Europe and the USA. The proportion is higher in some Asian countries (8% in Japan and 16% in south China) [2]. Although most FSs are apparently benign, one-third are prolonged or repetitive within 24 h; these are 'complex' and associated with a risk of subsequent temporal lobe epilepsy (TLE) [3]. Moreover, adults with TLE or mesial temporal sclerosis have a high prevalence (30%–50%) of FSs in childhood [4]. Conventional antiepileptic drugs are currently used to treat FSs. However, they are ineffective for subsequent epileptogenesis. Emerging research is identifying potential therapeutic targets for the prevention of FSs and also providing biomarkers that identify patients at risk of subsequent epileptogenesis. In this review, we first summarize the factors involved in the generation of FSs, including inflammation, brain pH, and genetic factors. The brain regions involved are also noted. Second, we describe the factors that contribute to the subsequent epileptogenesis. The relationship between these two issues is also discussed. Considering the importance of appropriate experimental models that mimic the pathophysiology of clinical FSs, we also briefly review the *in vitro* and *in vivo* models that have been used, along with a discussion of their advantages and disadvantages.

How Does Fever Trigger Seizures?

At a workshop on the subject of childhood convulsions with fever held in London in 1990, the working group defined "febrile seizures" as: "an epileptic seizure occurring in a child aged from six months to five years, precipitated by fever arising from infection outside the nervous system in a child who is otherwise neurologically normal."[5]. This definition distinguishes "febrile seizures" from "convulsions with fever". According to the definition, fever is an important factor that cannot be neglected. The causes of fever-induced seizures are multifactorial (see Table 1), including inflammation, brain pH,

✉ Zhong Chen
chenzhong@zju.edu.cn

[1] Department of Pharmacology, Key Laboratory of Medical Neurobiology of the Ministry of Health of China, School of Medicine, Zhejiang University, Hangzhou 310058, China

and genetic factors. Understanding the mechanisms will be helpful for the discovery of potential treatment targets to prevent seizures or to reduce recurrent FSs.

Inflammation

Although acute inflammatory responses can reduce the harmful effects of infection and tissue damage [6], excessive inflammatory responses lead to excitotoxicity [7]. Over the past two decades, it has been demonstrated that inflammation is involved in the pathogenesis of FSs (Table 1). However, the causal relationships among fever, cytokines, and seizures are not clear so far. In particular, studies have been focused on the pro-inflammatory cytokines released both peripherally and centrally during fever. For example, interleukin-1 beta (IL-1β) [8–10], tumor necrosis factor alpha (TNFα), interleukin-1 alpha (IL-1α) and IL-6 [11] increase during FSs not only in animals but also in patients. However, which is dominant among these cytokines during FSs? In 1990, Helminen and Vesikari, for the first time, reported an increase of IL-1β in lipopolysaccharide (LPS)-treated peripheral blood mononuclear cells from children with FSs [12]. Subsequent studies using animal models revealed that increased brain temperature leads to the synthesis of IL-1β both in the periphery and the CNS [13], so it was concluded that IL-1β, rather than other pro-inflammatory cytokines, contributes to the generation of FSs. Moreover, a cortical inflammatory response alone is capable of inducing focal seizures by increasing neuronal excitability through IL-1R1. For example, intra-hippocampal injection of IL-1β in wild-type mice reduces the FS threshold, while IL-1R1-knockout mice are resistant to this treatment [14]. Hence, it seems that fever induces the production and release of IL-1β, which subsequently triggers seizures. Seizures occur when the balance of neuronal excitation and inhibition is altered by neuronal inflammation [15]. More solid evidence from specific pharmacological or transgenic manipulations to target the synthesis and secretion of IL-1β is needed to clarify the causal relationship between FSs and IL-1β.

In turn, the seizure itself leads to inflammatory responses. Evidence from clinical observations and experiments shows that IL-1β contributes not only to the generation of FSs, but also to the epileptogenesis thereafter. Thus, IL-1β is a substantial factor in the initiation of seizures and it also plays a role in the aftermath of prolonged FSs. This is discussed in more detail in "Inflammation" section of this review.

Regulation and Modulation of pH in the Brain

A stable pH in tissues is essential for homeostasis. The acid-base balance influences neuronal activity by affecting a variety of ion channels and electrical activity which, in turn, elicit rapid pH changes [16]. The mechanisms that govern intracellular and extracellular H^+ are especially important in the brain. The occurrence of seizures is closely associated with pH fluctuations. This idea is supported by various experimental data. For example, the pH is lower during both *in vivo* (kainic acid and PTZ-induced) and

Table 1 Risk factors involved in fever-induced seizures.

	Animals/Regions	Human/Regions
In vivo		
Inflammation	IL-1β [14] lowers seizure threshold in rats.	Inflammation, no change/cerebral [70];
	IL-1β ↑/hippocampus [8, 38] and hypothalamus but not cortex [9];	HMGB1 and IL-1β, IL-6↑/serum [11] but no change in Ref. [71];
	mRNA of TNF-α and IL-6↑ /Hippocampus [11]	HMGB1/CSF [43];
		Neopterin↑/CSF [72];
		IL-1β and nitrite↑, but not TNFα/CSF [71];
		IL-1Ra/IL-1β ratio and IL-6↑/ plasma [10]
Brain pH	Respiratory alkalosis [18]	Respiratory alkalosis/systemic [19]
Genetics	Nav channel, β (1) mutant [73];	Interleukin-6 gene/blood; IL-1 Ra-I homozygote more frequent [76];
	GABRG2 (SNP211037)-C allele gene [74];	
	Missense mutations of SCN1A [75]	SCN1A mutant [56];
Others	Prenatal stress [27]	Iron deficiency [77], zinc [28] ↓/serum;
In vitro		
	GABABR-mediated inhibition ↓/cortex [85] and hippocampus [86]	

CSF, Cerebrospinal fluid; HMGB1, high-mobility group protein B1; IL-1 Ra, interleukin-1 receptor antagonist.

in vitro (low Mg^{2+}-induced) [17] seizure models. Moreover, Schuchmann *et al*. [18] have shown that hyperthermia leads to hyperventilation with an upregulation of 0.2–0.3 pH units (known as respiratory alkalosis), which contributes to the generation of experimental FSs. These seizures are completely prevented by exposing the mouse pups to 5% CO_2 in air. They further revealed that respiratory alkalosis also occurs in children with FSs [19]. However, whether fever induces respiratory alkalosis is still under debate. Baram's group [20] argued that the dramatic increase in body temperature is associated with little change in respiratory rate ($\sim$3%) before the onset of convulsions. Because the different models used are unable to explain their contradictory outcomes, Schuchmann *et al*. provided further evidence for a pronounced increase of respiratory rate in the "hair-dryer model" as well as the "heated chamber model". Hence, stronger evidence is needed to elucidate the relationship between hyperthermia and pH, and how pH changes trigger seizures. It can still be speculated that acid-base homeostasis is a potential target for studying the generation of FSs. Thus, regulating pH may be a potential strategy in the treatment of seizures and fever-related epileptic syndromes.

Temperature-Sensitive Cav1.2 Calcium Channels

FSs are triggered by hyperthermia, which may affect the excitability of the cerebral cortex. Patch-clamp recordings from hippocampal slices have shown that pyramidal neurons and interneurons are depolarized, fire spontaneously, and display a reduction in input resistance when exposed to hyperthermia [21]. These phenomena suggest that changes in intrinsic membrane excitability may play a critical role in FSs as well as in epileptic discharges. Radzicki and colleagues explored the underlying mechanisms, and found that the temperature-dependent intrinsic firing of cortical pyramidal neurons primarily depends on a nimodipine-sensitive Ca^{2+} current, mediated in large part by Cav1.2 subunits [22]. Thus, this temperature-sensitive Ca^{2+} current may be a pharmacological target for the treatment of FSs. Nimodipine has been shown to reduce the incidence and duration of seizures in FS studies *in vivo* [22]. Although there is no convincing evidence for the usefulness of nimodipine as an add-on treatment for epilepsy [23], inhibition of Ca^{2+} channels to affect the intrinsic firing induced by hyperthermia may be an alternative intervention for FSs.

Potassium Chloride Co-transporter 2

Excitation predominates over inhibition in the neuronal networks of the cerebral cortex and limbic structures during the neonatal period. During mammalian embryonic development, intracellular Cl^- concentrations are high due to low KCC2 (K^+-Cl^- co-transporter 2) expression and high levels of NKCC1 (Na^+-K^+-Cl^- co-transporter 1). During postnatal development, KCC2 levels are strongly upregulated while NKCC1 levels are down-regulated, resulting in a high level of extracellular Cl^-. More recently, a variant of SLC12A5, which encodes KCC2, was identified in an Australian family with FSs [24]. Further functional and structural analyses in rodent cortical neurons indicated that this variant results in an arginine-to-histidine substitution at position 952 in KCC2b, and brings about deficits in both neuronal Cl^- extrusion and the formation of dendritic spines. Previous studies have reported that genetic deficits in membrane KCC2 expression result in increased network excitability and higher susceptibility to epilepsy [25]. Even though there is no direct evidence linking the KCC2 variant with FSs, KCC2-R952H provides a novel molecular explanation for susceptibility to FSs.

Genetics

FSs are suspected to have a genetic component. The cause of FSs may be associated with two or more genetic factors that interact with environmental factors (Table 2). Identification of the genes involved in FSs will make a huge contribution to future research. And early detection of these susceptibility genes and appropriate intervention may prevent such seizures in children at risk. Twin and family studies point to an important genetic component in the etiology of FSs (*FEB1-11*; Table 3). *FEB1* on chromosome 8q13-21, *FEB2* on 19p13·3, and *FEB3* on 2q23-24, have been identified by parametric linkage analysis of a single large family. *FEB4* was found on 5q14-15 in a non-parametric analysis of a series of 47 small families [26]. Some families are not linked to any of these loci, highlighting the genetic heterogeneity in the monogenic forms of FS. Furthermore, mutations in genes encoding voltage-gated Na^+ channel subunits (SCN1A and SCN2A) and $GABA_A$ receptor subunits (γ2 and δ) have been identified in FSs. Thus, treatment with conventional drugs such as phenytoin and carbamazepine that block Na^+ channels are contraindicated for FSs associated with loss-of-function mutations in Na^+ channel subunits.

Many other risk factors contribute to the generation of FSs. The incidence of FSs is higher in infants, and the pathophysiological mechanisms of epileptogenesis in immature brain are rather different from those in mature brain. Therefore, the environment and experience of children during the prenatal and postnatal periods are crucial. An *in vivo* study has recently shown that exposure to prenatal stress may lead to an exaggerated FS response [27]. Other studies in humans also indicate that metals such as iron and zinc contribute to the generation of FSs [28]. Besides, neuronal activity is critical for synaptogenesis and

Table 2 Genetic factors contributing to febrile seizures.

Gene type		Mutation/variant	Coding sequence
Ion channels	Na^+ channels	SCN1A [56]	D188V; T875M; W1204R;
		SCN2A [78]	V1353L; GAL879-881QQQ
			R82Q; R43Q; Q390X; IVS6 + 2T→G;
			K289M and Q351X
Receptors	$GABA_A$	γ2 [79]	E177A
Gene polymorphisms	FEB1-11 [80]		
	IL-6	174 GG [81]	
	IL-1B	IL-1β (-511) allele 2 [82]	
	IL-1Ra	IL-1Ra allele I [83]	
		IL-1Ra intron 2 [29]	

Table 3 Genetic loci for febrile seizures in the OMIM (Online Mendelian Inheritance in Man) database.

Locus	Gene mutation	Chromosomal region
FEB1.		8q13-q21
FEB2.		19p
FEB3A.	SCN1A	2q24
FEB3B.	SCN9A	2q24
FEB4.	GPR98	5q14
FEB5.		6q
FEB6.		18p
FEB7.		21q22
FEB8.	GABRG2	5q31
FEB9.		3p24.2-p23
FEB10.		3q26
FEB11.	CPA6	8q13

spinogenesis during development. And abnormalities in dendritic spine number have been reported in brain tissue from epilepsy patients [29]. Therefore, the specific status and the immaturity of the brain cannot be ignored when investigating how fever induces seizures. Conditional transgenic mice and other techniques are needed to clarify this problem.

Do Prolonged Febrile Seizures Cause Epilepsy? If So, How?

Although brief or simple FSs have no significant effect on neuronal function (as measured by cognitive tests) or on the probability of developing epilepsy, several retrospective clinical studies have demonstrated a significant relationship between a history of complex FSs and mesial temporal sclerosis, which is responsible for intractable TLE [4]. In addition, animal models of prolonged FSs have also been used to address these issues. Brains from rats that experienced prolonged FSs show a lower seizure threshold to excitatory input both *in vivo* (kainic acid) and *in vitro* (electrical stimulation), and 100% of them show generalized seizures when treated with a sub-threshold of kainic acid [30]. And 35%–45% of these develop spontaneous TLE with typical changes in the hippocampus as well as the cortex [8, 31]. It is worth noting that febrile status epilepticus lasting longer than 30 min or a series of shorter seizures, from which the infant fails to regain consciousness inter-ictally, may potentially modify the immature brain [32]. This modification may further contribute to long-term epileptogenesis. Investigation of this speculation might be very useful to the study of epileptogenesis after complex FSs.

Then what happens during the period from childhood to adulthood after complex FSs? Studies have demonstrated that both pre- and post-synaptic functions undergo long-term changes after complex FSs. One study revealed a persistent, presynaptic, and protein kinase-A-dependent enhancement of perisomatic GABAergic transmission in CA1 pyramidal cells in brain slices from neonatal rats with FSs [33]. Besides, intrinsic membrane depolarizing currents such as hyperpolarization-activated cyclic nucleotide-gated channel (HCN, I_h) are persistently modified by prolonged FSs in rats [34]. The risk factors involved in epileptogenesis after complex FSs are summarized in Table 4.

Inflammation

Inflammatory responses induced by brain damage, such as trauma, stroke, infection, febrile seizures, and status epilepticus, are associated with acute symptomatic seizures and raise the risk of epileptogenesis in later life [35]. Moreover, neuroinflammation appears to be a prominent feature in the mesial TLE syndrome in both patients and animal models [36]. Among numerous cytokines, IL-1β has attracted considerable attention because of its relationship with epileptogenesis after prolonged FSs. IL-1β is

rapidly upregulated during seizures in glial and endothelial cells in the epileptic focus as well as in forebrain regions [37]. It transiently increases within 24 h after prolonged FSs, and then returns to baseline [8, 38]. An alteration in the ratio of IL-1β/IL-1ra in the hypothalamus and hippocampus after FSs has also been reported [9]. Our recent data showed that pro-IL-1β decreases while cleaved caspase-1 and IL-1β increase immediately following prolonged FSs, suggesting that the transient increase in IL-1β is a result of the increased breakdown of the immature to the mature form mediated by caspase-1 activation [38]. Moreover, mRNA of IL-1β is overproduced in the hippocampus at the onset of the convulsion [39], so transcriptional activation of the IL-1β gene may be part of the subsequent IL-1β modification. If the change of IL-1β in early life indeed enhances the susceptibility to seizures in later life, identification of the downstream molecules or pathways that undergo a long-term change and increase neuronal excitability is a challenging and interesting direction for future studies [38, 40]. In addition, since burns caused in animals by hyperthermia may produce a peripheral inflammatory reaction and increase inflammatory factors, the influence of exogenous inflammation should be excluded by using appropriate animal FS models.

Inflammation induced by fever has both deleterious and beneficial effects on neuronal function (Fig. 1). For example, IL-1β increases the synthesis of inhibitory peptides and neurotrophic factors to protect neurons. Simultaneously, however, increased IL-1β mRNA and protein in the brain promote several forms of neuronal damage, including seizures. Moreover, excessive inflammation not only has direct effects on target tissues, but also induces the production of additional mediators and activates other pathways [41], such as the Toll-like receptor pathway. If these mediators and pathways are relevant to synaptic function or neuron/glia-sensitive, they could further enhance the long-term neuronal excitability (lasting to adulthood). More solid evidence is needed to test this speculation.

In addition to IL-1β, high-mobility group protein B1 (HMGB1), a cytokine mediator of inflammation that is secreted by activated macrophages and monocytes, is considered to be associated with epilepsy. By using models of acute and chronic seizures in C57BL/6 mice, Vezzani *et al*. demonstrated a pro-convulsive pathway involving HMGB1 release and its interaction with Toll-like receptor 4 (TLR4). The expression of HMGB1 and TLR4 is increased in mice with kainic acid-induced epilepsy as well as in human epileptogenic tissues [42]. A study of children who suffered a 30-min febrile seizure has demonstrated significantly higher expression of HMGB1 and other pro-inflammatory cytokines [43]. Therefore, all this evidence suggests that pro-inflammatory cytokines are crucial for the epileptogenesis after prolonged FSs.

Endocannabinoid System

The endocannabinoid system tightly controls neuronal excitability and synaptic plasticity. This system is a retrograde signal to inhibit transmitter release from the presynaptic membrane triggered by a transient depolarization of the postsynaptic neuron [44] (Fig. 2). This phenomenon is known as 'depolarization-induced suppression of inhibition' in GABAergic interneurons and 'depolarization-

Table 4 Factors contributing to epileptogenesis following complex febrile seizures.

	Regions
In vivo	
Inflammation	IL-1β↑/epileptic focus and forebrain [8, 38];
	HMGB1↑/neurons and glia [42, 43]
Brain temperature	Hyperthermia decreased peak amplitude of $GABA_A$ IPSCs/PCs but not GCs [84]
Cognitive function	Cognitive and behavioral deficits [85]
Cannabinoid system	Depolarization-induced suppression of inhibition (DSI)↑ CB1R expression↑/hippocampus [47]
Others	Long-term $GABA_AR$ β2/3 expression↑/newborn DG cells [86]
	$GABA_A$α1 subunit↓, α2 subunit↑, NKCC1/KCC2 ratio↑/sensorimotor cortex [87]
	NMDAR-mediated EPSC population of newborn cells that survive and mature into EAAT3-positive neurons↓[88]
	$GABA_B$ receptor-mediated inhibition↓ [89] *H*-channels↑ [34]
In vitro	
Cannabinoid system	DSI↑/hippocampus [48]

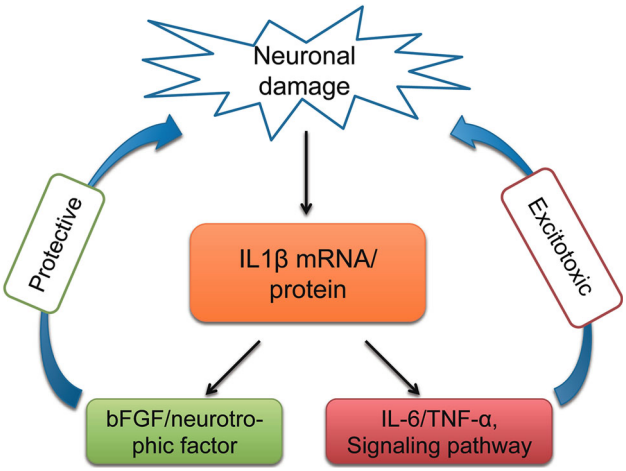

Fig. 1 IL-1β production induced by neuronal damage has both beneficial and deleterious effects on neuronal function. It increases the synthesis of inhibitory peptides and neurotrophic factors to protect neurons. However, excessive IL-1β mRNA and protein in the brain activate other pathways that have deleterious effects, such as increased neuronal excitability.

induced suppression of excitation' in glutamatergic neurons. Whether activation of the endogenous cannabinoid system is protective or neurotoxic during seizures is still under debate. Exogenous natural and synthetic cannabinoids exert neuroprotective actions in several models of neurotoxicity, and endocannabinoids protect against epileptic symptoms [44]. And the presence of CB1 (cannabinoid receptor type 1) receptors in glutamatergic hippocampal neurons is necessary and sufficient to provide substantial endogenous protection against acute excitotoxic seizures [45]. However, Δ9-tetrahydrocannabinol, the principal psychoactive constituent of the cannabis plant, has been reported to induce hippocampal neurotoxicity [46]. Besides, endocannabinoid-mediated suppression of GABA (but not glutamate) is increased in the long-term after prolonged FSs [47]. This is possibly due to a persistent upregulation of CB1 receptors on principal cells in the hippocampus. Accordingly, application of the CB1 receptor antagonist SR141716A (also known as Rimonabant) before FSs can inhibit the seizure-induced potentiation of the depolarization-induced suppression of inhibition, abolish the seizure-induced upregulation of CB1 receptors, and prevent long-term limbic hyperexcitability [48]. Although this antagonist is considered to be an acute proconvulsant, it prevents the chronic enhancement of limbic hyperexcitability induced by prolonged FSs. CB1 receptor activation suppresses both GABA and glutamate release. It is possible that the CB1 receptors on GABAergic and glutamatergic neurons are activated separately in response to different depolarizing stimuli, or may be age-dependently activated by such stimuli. Further work is needed to

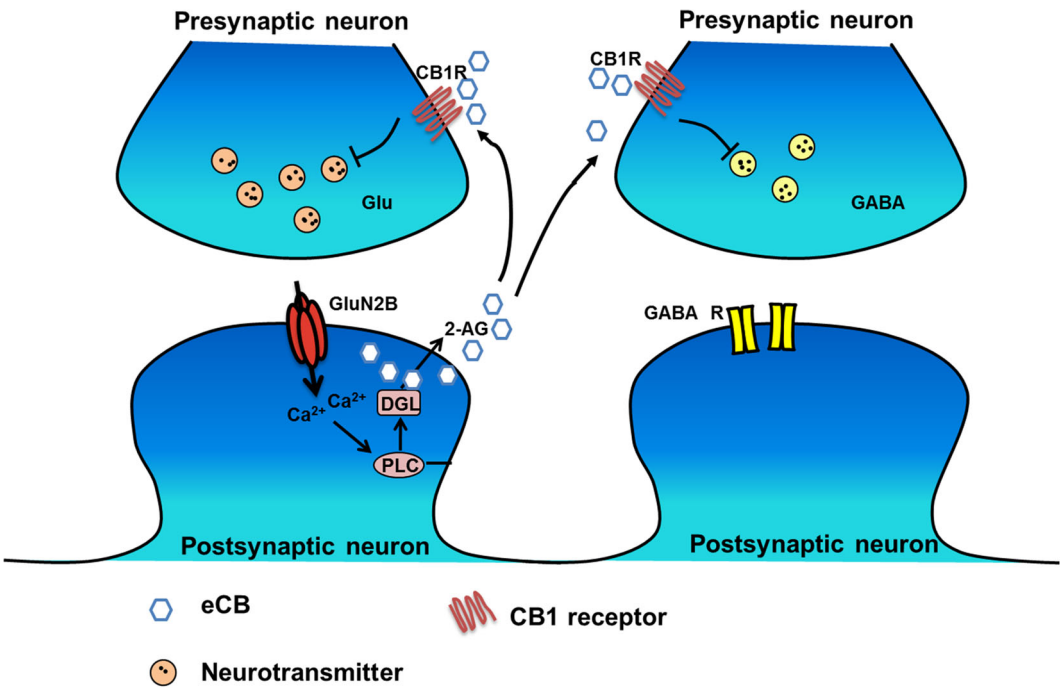

Fig. 2 Endocannabinoid system mediates retrograde signaling. When a transient depolarization triggers the postsynaptic neuron, endocannabinoids are synthesized in the postsynaptic neuron and released into the synaptic cleft through transporters. Then the activation of CB1 receptors located in the presynaptic membrane inhibits neurotransmitter release from the presynaptic membrane. This phenomenon is termed 'depolarization-induced suppression of excitation' in glutamatergic neurons (left panel) and 'depolarization-induced suppression of inhibition' in GABAergic interneurons (right panel). Glu, glutamate; 2-AG, 2-arachidonoylglycerol; DGL, diacylglycerol lipase; PLC, phospholipase C.

determine exactly what kind of CB1 receptor-dependent signaling system is most beneficial under different conditions. It is worth noting that although CB1 receptors are expressed at a high level in neurons throughout the brain, functional CB1 receptors have also been detected in astrocytes. Recently, Xia's lab has highlighted that it is the activated astroglial CB1 receptors that impair spatial working memory [49]. Hence, although the expression level of CB1 receptors in astrocytes is low, their function cannot be ignored in future studies.

HCN Channel

The HCN (I_h), also referred to as the "pacemaker" channel, belongs to the superfamily of voltage-gated K^+ (Kv) and cyclic nucleotide-gated channels. The HCN channel is encoded by four genes (HCN1-4; Fig. 3) and is found in neurons and cardiac cells, playing functional roles in the heart and in sleep rhythms in thalamo-cortical neuronal circuits [50]. It has also been implicated in the transmission and integration of excitatory synaptic inputs. Moreover, presynaptic HCN channels contribute to age-specific neuronal firing properties and the expression of HCN1 in perforant path axon terminals declines with age [51]. In more detail, HCN1 channels are localized to axon terminals of the perforant path in immature rats, but their presynaptic expression and functions disappear with maturation [52]. Because of the special characteristics of HCN channels in excitability modulation and their contributions to hippocampus maturation, these channels have drawn increasing attention in the area of nervous system diseases, especially in developmental diseases such as FSs. Indeed, Chen *et al*., in 1999 showed that an increased I_h current occurs after FSs [33]. The enhancement of I_h current converts potentiated GABA-mediated synaptic inhibition into hyperexcitability [53]. These findings may provide a solution to the long-standing paradox of increased inhibitory GABAergic synaptic transmission and a lower epilepsy threshold after prolonged FSs. In contrast, Ouardouz *et al*. compared the consequences of FSs with dysgenesis (cortical freeze lesion) and FSs alone [54]. They found that changes in I_h are less pronounced in FSs with dysgenesis than FSs alone, while the increase in $GABA_A$-mediated inhibition is comparable in rats with or without dysgenesis after FSs. Therefore, the former hypothesis that the long-lasting increase of I_h converts the potentiated synaptic inhibition to hyperexcitability cannot explain the higher incidence of adulthood recurrent seizures in rats with dysgenesis than those without

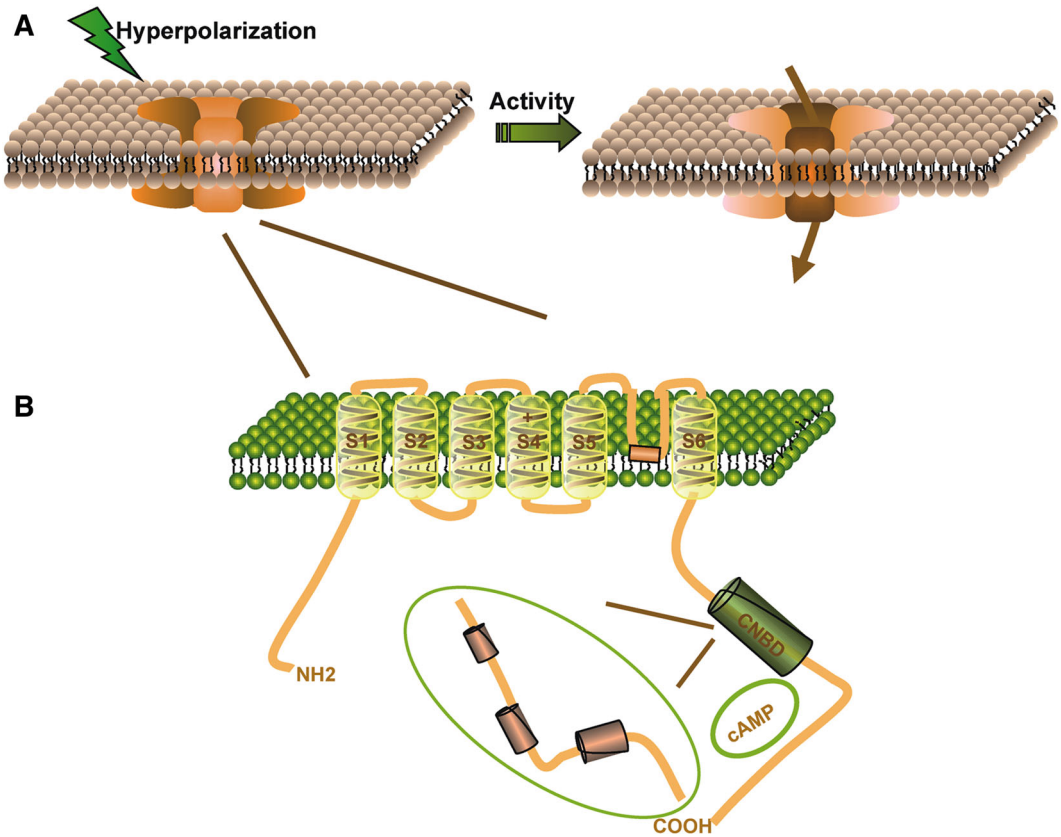

Fig. 3 Cartoon of the HCN channel. A. The channel is activated by hyperpolarization resulting in a positive shift of I_h current. B. One subunit of the channel is composed of six transmembrane domains (S1-S6), among which S4 is the putative voltage sensor that has an intracellular N-terminal region and a cytoplasmic C-terminal region containing a cyclic nucleotide binding domain (CNBD).

dysgenesis after FSs. Since inhibition of I_h increases the amplitude of evoked and simulated excitatory postsynaptic currents [55], the changes in I_h may dampen the N-methyl-D-aspartate (NMDA) receptor-mediated hyperexcitability after FSs, rather than converting inhibition into excitation. Understanding the complex interaction among I_h, NMDA, and GABA conductance after FSs is of particular significance for the development of specific therapeutic strategies in children who suffer FSs, and in patients with TLE and a past history of FSs.

Genetics

Generalized epilepsy with febrile seizures plus (GEFS+) is the archetypal disorder with a familial association of FSs and epileptic seizures and is inherited as an autosomal dominant trait. So far, several disease-causing genes, such as SCN1B, SCN1A, and GABRG2, have been shown to be involved in GEFS+ [26]. The SCN1B mutation is mapped to the chromosome 19q13·1. A mutation (C121W) in the auxiliary β1 subunit of the neuronal voltage-gated Na^+ channel has been identified in an Australian family. This mutation probably changes the tertiary structure of the protein by disrupting a disulfide bridge. The SCN1A mutation has been mapped to the 2q21-33 region and has been identified in patients with a variety of epilepsies, of which those with antecedent FSs are the most common. Functional studies of SCN1A mutations have demonstrated that functional alteration of the expressed protein is directly linked to the phenotype [56].

Experimental Febrile Seizure Models

Clinical and experimental studies of FSs have provided numbers of potential targets for the issues discussed above. However, an obvious drawback in clinical studies on FSs or their relationship to subsequent epileptogenesis is that it is difficult to distinguish the influence of preexisting brain pathology (e.g. genetic or acquired factors) and treatment (e.g., side-effect of drugs) from the FS itself (e.g., seizure type, number, and duration). Thus, controversy over the clinical outcomes and the important role of FSs makes it necessary to develop proper animal models that facilitate our understanding of the pathophysiology of FSs and their relationship with TLE (Table 5).

The different FS models used in earlier studies have advantages as well as shortcomings. One of the most critical factors is the age of animals and the other is the heat source. Hjeresen and Diaz developed a rat model using microwaves as the heat source. They demonstrated that rats on postnatal days 10–17 were susceptible to FSs but without corresponding EEG recordings [57]. In another model described by Morimoto *et al*., heated air was used to induce seizures with EEG confirmation [58]. However, they used rats on postnatal days 24–29, significantly older (given the species differences in development) than human infants [59]. Younger animals have higher mortality and atypical behaviors [60]. Baram [61] found that the onset threshold of hyperthermia-induced seizures varies markedly among individual 6–7-day-old rats. In addition to age, the heat source dramatically affects the behavior and mortality. Infrared irradiation, microwaves, heated/warm air, and warm water have been used as heat sources. Since microwaves, warm water, and infrared irradiation harm animals, heated air seems to be a satisfactory source. Another approach that has been used is to combine LPS with a subthreshold dose of kainic acid [62]. However, as the definition states that seizures are not considered to be "febrile seizures" when they occur with fever but in the context of exposure to pro-convulsive drugs [63], this model may not correspond to FSs in the strict sense.

Baram and collaborators developed a well-established experimental FS model in 1997. In this model, rat pups are placed in a glass container with heated air blowing on the top [61]. A hair dryer is used to raise the surrounding temperature

Table 5 Experimental models of febrile seizures.

	Species	Postnatal days	Heat source	References
In vivo	Rat	2–10	Infrared lamp	[60]
	Rat	13–17	Microwave	[90]
	Rat	26–29	Warm air	[91]
	Rat	15	Ambient	[92]
	Rat	6–7, 8–9, 10–12	Heated air	[61]
	Rat	22	Water	[93]
	Rat	14	Lipopolysaccharide	[62]
	Mouse	10–14	Warm air	[66]
	Zebrafish	3 to 7	Water bath	[67]
In vitro	Hippocampal slices			[68]
	Cultured rat cortical neurons			[94]

to the 43.5–44.5 °C range in order to maintain the core temperature around 42.5 °C. According to this model, seizures are induced reliably and are most stereotyped in the 10–11-day-old rat, an age considered to best correspond to that of human infants who are most susceptible to FSs [57]. Schuchmann *et al*. [19] developed another animal model using a warm chamber as the heat source to raise the body temperature to an appropriate level. In our study, we chose the latter because we found that the warm chamber has lower mortality and fewer burns than heated air [38, 40, 64, 65]. Besides, Dube *et al*. [14] and Gassen *et al*. [66] used mouse FS models, facilitating the use of genetically mutant mice and other specific techniques.

Recently, an animal model of hyperthermia-induced seizures in larval zebrafish was developed [67], extending *in vivo* FS models from rodents to vertebrates. And as a model biological system, the zebrafish has numerous advantages. Its genome has been fully sequenced, and its developmental behaviors are well-understood, easily observable, and testable. Furthermore, well-characterized mutant strains are readily available. In addition to *in vivo* models, some *in vitro* models have also been developed, making it more convenient to study the issues discussed above. Tancredi *et al*. first demonstrated hyperthermia-induced epileptiform activity in hippocampal slices from immature rats [68].

Although experimental FS models have limitations that mean they are not exactly the same as the phenomena seen clinically, such models have their own advantages. They not only help to uncover the mechanisms underlying the generation of FSs, which are difficult to assess in the clinic, but also suggest how complex FSs might affect later-life outcomes, such as long-lasting modulation of synaptic plasticity and memory dysfunction [69]. Given the differences between clinical and laboratory studies, experimental animal models may not completely imitate clinical conditions. Therefore, models that are closer to the clinic with lower mortality need to be developed in order to guide clinical treatment.

Conclusions

FSs affect 2%–4% of children worldwide. The underlying mechanisms and the consequences of these seizures have been a focus of interest for pediatricians and researchers. Clinical and experimental studies have revealed some key factors in the generation of FSs. Among them, inflammation is at the fore. It is implicated in the generation of FSs as well as in the relationship between FSs and TLE. In addition, data accumulated from well-established experimental animal models have provided invaluable information for clinicians as well as developmental and functional neurobiologists. Although FSs are mostly benign, and only a minority of children who suffer prolonged and complex FSs develop epilepsy later, it is still important to determine the neurologic status before and after any seizure occurs. Such studies might be very useful for the clinical treatment of epilepsy. Besides, the definition of FSs excludes infections in the central nervous system, but does not exclude those in the periphery. Whether children with recurrent FSs without evidence of a history of afebrile seizures had suffered severe trauma or infections might be an important evaluation index. Furthermore, as children who experience recurrent and prolonged FSs have a risk of developing TLE in later life, it is crucial to reduce the recurrence of FSs in a timely and effective manner. However, the antiepileptic drugs commonly used to treat FSs fail to reduce the risk of epileptogenesis after FSs. Hence, it is necessary to elucidate the mechanisms underlying the generation of infantile FSs and the subsequent epileptogenesis in further studies.

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