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Chapter 11

Experimental models of febrile seizures and febrile status epilepticus

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The need for animal models: They provide causality and mechanisms

There has been a growing body of literature in the fields of epidemiology, genetics, epigenetics, and imaging focusing on understanding febrile seizures, but many of the key questions related to mechanisms are incompletely understood. Prospective and case-control studies have looked at risk factors for simple and complex febrile seizures [1–6], but the nature of these human studies provides only correlative insight. Animal models, on the other hand, enable testing of the causal relation between specific genetic mutations and febrile seizures (FS) and between long febrile seizures and subsequent epilepsy. They allow for the

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independent investigation of the complex contributions that predisposing genetic mutation and inciting febrile seizures have on the developmental of limbic epilepsy, an impossibility in children. Additionally, emerging novel technologies have been developed for probing molecular, cellular, and circuit functions. These technologies have facilitated greater knowledge of the pathogenesis surrounding febrile seizures including transcriptional, epigenetic, and inflammatory changes, circuit mechanisms of epileptogenesis and long-term cognitive problems, and magnetic resonance imaging (MRI) predictive markers.

A host of animal models have been developed over the years to tackle the difficulties of studying the mechanisms of febrile seizures and their potential direct effects on the developing brain. Here we discuss these animal models from various perspectives. First, we discuss genetic animal models based on both known and novel predisposing mutations and the tools they employ to probe the underlying mechanisms. Next, models of single, recurrent, and complex febrile seizures will be illustrated. We will review several methods of generating FS and febrile status epilepticus (FSE). Finally, we will conclude with what these models have taught us and what they cannot teach us.

Considerations and choices of animal models

Animal models used for the study of human conditions, such as febrile seizures, are essential to established causality among related observations and probe novel mechanisms and therapies for these disorders. However, models, by their nature, can only approximate the actual condition, and features of the model itself dictate the questions that can be addressed. For example, genetic background, animal type, and hyperthermic induction methods may offer specific and distinct answers to those questions.

Choice of species and "background" genetics

Rodent models provide serious advantages in short life spans and access to study the brain directly as described above. Their mammalian brain is also relatively similar in molecular, cellular, and circuitry aspects to the human brain. Thus, it is not surprising that most FS models involve rodents, though there are some other species that have been studied. Notably, several groups capitalized on the assets of zebra fish [7,8], drosophila [9–11], and even chicks [12] to study FS. Within rodents, rats began as the canonical paradigm; yet, with the advent of genetic tools in the mouse, numerous studies involving mice have surfaced, probing both the genetic basis of FS and the involvement of specific molecules, pathways, and brain circuits.

Genetic strains of mice differ in seizure-threshold temperatures [13] and profiles of resilience and susceptibility to the induction of acute seizures by "febrile seizures" [14]. Spontaneous seizure generation in transgenic mice has a notable dependence on genetic background [15]. Extensive studies have

shown that genetic background plays an important role in affecting seizure thresholds in mice [16–18], with strains such as the C57BL/6 strain being more resistant to systemic administration of kainic acid than ICR, FVB/N, and BALB/c strains [16,19,20]. However, even substrains within C57BL/6 mice vary in sensitivity to chemoconvulsants [21]. Some authors have reported greater susceptibility of the C57BL/6 strain to febrile seizures [22], despite having greater resistance to chemoconvulsants. With distinct genetic strain and substrain differences in the context of chemical, electrical, and hyperthermic seizure induction, the type of animal model used must be carefully considered.

The threshold temperature required to induce FS in mutant organisms provides a good measure of the contribution of the mutation to overall hyperexcitability and likely to the generation of FS. For example, specific SCN1A mutations reduce the temperature at which mice develop tonic hyperthermic seizures [23]. This observation is not limited to mice. Drosophila mutants with a SCN1A S1231R mutation exhibit spontaneous and heat-induced seizures with lower onset temperature than GEFS + flies [9]. Subtle strain differences have been measured in stress responses and cognitive performance in behavioral studies of rats [24], reinforcing the importance of a careful consideration of rodent strain when selecting the appropriate animal model.

Age

Another crucial consideration to address is the choice of age used to model febrile seizures. Febrile seizures are seen in infants and young children between 6 months and 6 years of age, with a peak incidence of ~ 18 months [25,26]. It is thus appropriate to correlate rodent to human brain development to model the developmental window that human infants and young children are most susceptible to febrile seizures. This is important to enable the translation of studies in animals to human interventions. The developing brain, however, is complex in nature, as specific regions and circuits mature with variable velocities and at specific time points [27]. The precise rates of development vary across species, making correlations in brain development only an approximation. Comparative analysis of hippocampal formation in human and rodents, while they cannot precisely correlate human and rodent "ages," they do suggest that the first week of life in rats (days 0–5) may be comparable to third-trimester gestational period in humans and days 7–14 in rats correspond to roughly the first year of human life [28]. This developmental time line might differ for thalamo-cortical and other cortical-subcortical circuits [29]. Thus, most experimental models of FS are induced in rats during the 7–14 postnatal day window [30–32].

In mice, some groups identified postnatal days 14–15 as optimal for induction of FS [22,33–35]. Others have chosen somewhat older ages [13]. As in rats, precise correlation of brain development across mice and humans is complex,

and the regions involved in the generation of FS may mature at different ages across species. Notably, age has not been a major consideration in zebra fish [7] or drosophila [9] models.

Genetic animal models of febrile seizures and related syndromes

The development of genetic tools and their evolution has had a dramatic effect on the study of FS and related genetic syndromes. The identification of Dravet syndrome and its common association with mutations of the voltage-regulated sodium channel gene Scn1a (Nav 1.1) has led to a flood of scientific effort to determine why and how these mutations lead to the phenotype. This initial work was followed by the discovery of other mutations related to the same channel with differing phenotypes, as well to a plethora of additional ion channel and neurotransmitter receptor mutations promoting FS-related diseases.

Further, these mutations have been inserted into the salient gene in mice, rats, flies, and zebra fish, as well as expressed in high-throughput systems such as xenopus oocytes. More recently, several mutations have been combined in the same system or mouse, to probe their interactions.

Tables 1A–1C aim to provide a compendium and resource of these studies, though the authors apologize if we neglected an important contribution. The table is organized as follows: Table 1A: known predisposing mutations in SCN1A (Dravet syndrome/severe myoclonic epilepsy of infancy [SMEI]). Other mutations involved in these syndromes follow in Table 1B (e.g., in GABA-A receptor subunits). We then include recent work on other ion channel genes including the TRP and HCN channels as well as genes involved in thermoregulation, in Table 1C.

Models of simple FS, recurrent FS, FSE, and epileptogenesis

In infants and children, simple FSs have excellent outcomes, whereas recurrent FS and especially FSE have more guarded outcomes, as discussed throughout this book. Therefore, an important distinction is made between models of short FS, recurrent FS, and prolonged FS constituting febrile status epilepticus (FSE). These distinctions are highlighted in Table 2.

Generation of simple, short FS is often used as a tool to probe mechanisms governing brain excitability. For example, the threshold temperature required to generate these seizures in a genetically engineered mouse or fly provides information about how the mutation influences the propensity to develop FS and perhaps excitability in general. Similarly, threshold temperature to FS has been used after random mutagenesis as a screen for mutations altering brain excitability. Threshold temperature for experimental FS is also used as a drug screen for anticonvulsants and other agents.

TABLE 1A SCN1 mutations.

Mutation	Method	Species	Notes	References
SCN1A: SMEI mutation, targeted deletion of the last exon	Loss of function mutation: SCN1A $^{-/+}$ and SCN1a $^{-/-}$;	129/SvJ and C57BL/6 mice	Spontaneous seizures and death begin on P21; genetic background important FS protocol from Oakley 2009; [36,37]	[36–39]
SCN1A: SMEI mutation: targeted deletion of last exon	SCN1A$^{+/-}$ mice Modification of [39]	C57BL/6 mice 10 generations	Body temperature elevated by 0.5°C every 2 min until seizure occurs or 42.5°C FS protocol from Oakley 2009 [40]	[13,40,41]
SCN1A: SCN1A-R1407X (human SMEI mutation)	Knock-in (KI) mouse line	C57BL/6/129 (~75%/25%) mice	Mice developed seizures within first postnatal month	[42,43]
SCN1A: KO of SCN1A allele	Scn1a^Flox/+/ZP3-Cre$^{+/-}$ Scn1a^Flox/+/EMX-Cre$^{+/-}$ Scn1a^Flox/+/Ppp1r2-Cre$^{+/-}$	Lines maintained on C57BL/6J background	Preferential inactivation of Scn1a in corticolimbic PV interneurons reduces latency to hyperthermia-induced seizures FS protocol from Oakley	[40]
SCN1A: human GEFS+ mutation	Targeted R1648H mutation SCN1A-R1648H with SCN2A KCNQ2 and SCN8A	FVB/NJ bred to C57BL/6J C57BL/6NCrl females x (C57BL/6J X DBA/2J); F1 males	R1648H transgenic mice have lower seizure thresholds Hets with rare seizures, reduced threshold, and accelerated propagation of FS	[23,41,44–47]
SCN1A: two truncated mutants, R222* and R1234*	Mutations cause premature termination	Hippocampal neurons dissociated from KO mice	Recordings from hippocampal neurons	[48]

Continued

TABLE 1A SCN1 mutations—cont'd

Mutation	Method	Species	Notes	References
SCN1A: exon 1 containing the translation start site replaced by a selection cassette	Scn1a^tm1Kea	129S6/SvEvTac, C57BL/6J mice	C57BL/6J × 129S6/SvEvTac strain Scn1a $^{+/-}$ mice exhibit spontaneous seizures and early lethality	[49]
SCN1A: Scn1a (E1099X/+) mutation	Scn1a^E1099X	C57BL/6JNar, 129S2/SvPasCrl mice	Scn1aE1099X/+ mimics genetic deficits of human Dravet syndrome. Het mice have early seizures and susceptibility to FS Cheah 2012 protocol	[50]
SCN1A: SMEI mutation: exon 25 removed	GABAergic cells conditional KO lines: C57BL/6 F/F mice x Dlx-Cre+	C57BL/6:CD1 mice	FS induction at P22 increased temperature in 0.5°C steps each 2 min until seizure or 42°C	[51]
SCN1A: deletion of coding exon 7 of SCN1a allele	GABAergic cells conditional KO lines: deletion in inhibitory neurons	C57BL/6:129 mice		[52]
SCN1A: Dravet A1783V mutation	Knock-in mouse	C57Bl/6J mice		[53]
SCN1A: missense mutation (N1417H)	Gene-driven ENU mutagenesis	Wistar rats	Scn1a mutant rats exhibit high susceptibility to experimental FS FS protocol water bath (Mashimo 2010)	[54–56]
SCN1A: two alleles of the didy mutant, didys552, and didys390	Double indemnity (didy) mutant disrupts voltage-gated Na channel	Zebra fish	*Didy* mutation disrupts the voltage-gated sodium channel Scn1lab (Nav1.1b)	[8]

SCN1A: Nav1.1 (scn1Lab) mutants: meth to Arg mutation in domain III	Scn1Lab (didys552) zebra fish embryos	Zebra fish	Zebra fish scn1Lab gene shares a 77% identity with human SCN1A and is expressed in the CNS	[57]
Para, shi, and com reversible, temperature-sensitive paralytic mutants	Temperature-sensitive paralytic mutant of Drosophila, comatose generated from wild-type strain, Canton-Special	*Drosophila melanogaster* Drosophila	Para, shi, and com exposed to 38°C for 1 min Para mutant is paralyzed quickly, recovers quickly at 23°C. Com mutant takes longer to pass out and recovers much slower. Shi mutant is intermediate	[10]
SCN1A: bss1 GOF mutation in the para Na+channel gene	Bang senseless (bss); allele of the paralytic (para) voltage-gated Na(+) channel gene	Drosophila	Bss-associated "seizures"	[11]
SCN1A: knock-in of a GEFS+ SCN1A mutation (K1270T)	Drosophila KI flies; K1270T mutation in Na channel gene, para	Drosophila	Temperature-dependent shift in Na+current deactivation exacerbated by the mutation. May contribute to GEFS+	[9]
SCN1A: Dravet syndrome (DS) SCN1A mutation (S1231R)	Introduction of DS mutation (S1231) into Drosophila gene para	Drosophila	Spontaneous and heat-induced seizures. Lower threshold temperature than GEFS+ flies	[58]
SCN1B: $GEFS^{+}$ C121W β1 Na+channel mutant	KI mice with β1(C121W) mutation	C57BL/6 mice	Het β1(C121W) mutant mice recapitulate FS of patients with mutation	[59]
SCN1A SMEI mutation (last SCN1A exon replaced with neomycin and SCN8A mis-sense mutation)	$Scn1a^{+/-}$; Scn8amed-jo/+ double hets; $Scn1a^{-/-}$; Scn8amed-jo/+ mutants	C3HeB/FeJ and C57BL/6J mice	Scn8a functions as a genetic modifier of SMEI	[60]
SCN9A: N641Y mutation	N641Y mutation into orthologous mouse gene to create a knock-in mouse	C57BL/6J mice	Scn9a-N641Y KI mice do not have spontaneous seizures	[61]

TABLE 1B Other mutations involved in dravet syndrome/severe myoclonic epilepsy of infancy (SMEI).

Mutation	Method	Species	Notes	References
GABAA R mutation: GABAA γ2(R43Q)	GABAA γ2(R43Q) mutants; homologous recombination	C57BL/6 or DBA/2J mice	Seizure onset at P20	[62,63]
GABRG2: Q390X mutation	Gabrg2 $^{+/Q390X}$ knock-in mouse (Kang 2014, Warner 2017) Gabrg2 $^{+/-}$ KO mouse	C57BL/6J N8–10 and DBA N8 mice		[15,64,65]
GABAA-receptor γ2-subunit: Q351X mutation	Discovered by genetic screen of patients with GEFS+, FS, and IGE. Premature stop codon at Q351 in the mature protein	*Xenopus laevis* oocytes	Q390X is also Q351X when not including 39 amino acid signal peptide	[66]
α1β2γ2 receptors with γ2 R43Q, K289M, Q351X	All point mutations were made using a site-directed mutagenesis kit	Xenopus		[14]
GABRG2 (encoding the γ2-subunit): R43Q mutation	Mutation derived from a screen of a family with absence epilepsy and FS GABAAγ2(R43Q) knock-in and GABAAγ2 $^{+/-}$ heterozygous knockout	DBA/2J and C57BL/6J mice	Seizures with lower latency than WT; FS protocol from Schuchmann 2006	[67,68]
K289M mutation in (GABRG2)	From family with GEFS+	Xenopus		[69]
GABARG2: p.R139G mutation	Diagnostic genetics of patients FS, GEFS+, absence		Mutation produced only FS	[70]
GABRG2:	Several GABRG2 mutations related to GEFS+ R82Q, P83S N79S			[71,72]

TABLE 1C Mutations in other ion channel and genes involved with thermoregulation.

Mutation	Method	Species	Notes	References
HCN1	Mice endowed with human mutations in HCN1 have neonatal epileptic encephalopathy			[73,74]
HCN1	Mice endowed with diverse human HCN1 mutations have a spectrum of epilepsies			[75,76]
TRPV	Temperature-dependent transient potential channels Trpv1 –/–	Mouse		[77,78]
TMEM16C (ANO3)	Tmem16c KO in rat pups and Tmem16c cKO in mouse pups	C57B6/129SvJ mice; rats	KO rat pups have rapid temperature rise upon heat exposure. KO mice pups have poor thermoregulation Both had greater susceptibility to FS	[79]

TABLE 2 Animal models of febrile seizures, including murine, chicks, and zebrafish.

Method	Age	Species	Notes	References
A. Single-short febrile seizure				
250W infrared lamp	P2–P10	Sprague-Dawley rats	Increased resistance to HS with maturation and electrocortical discharges similar to those in young children Heating duration: until seizure activity appeared	[80,81]
250W infrared lamp	P5–P20	Sprague-Dawley rats	A single hyperthermia convulsion (HC); 5, 10, 15, or 20 days of age Heating duration: until convulsion appeared	[82]
250W infrared lamp	P15	Long Evans rats	Experimental adults have reduced anticonvulsant response to a benzo-diazepam when given PTZ Heating duration: until full tonic extension occurred	[83]
56W infrared lamp	1: P23–P26 2: P20–P25	Lewis rats	Hypoxia significantly increased seizure threshold and hyperoxia prolonged seizure duration	1: [84] 2: [85]
660W infrared lamp	P15	Long-Evans rats	HS decreases GABA B receptor-mediated inhibition in hippocampus Heating duration: until core temperature reached 41–43°C	[86]
Heated chamber	1: P26–P29 2: P24–P26 3–4: P23–P24	Wistar rats	Arrest of locomotion concurrently with paroxysmal EEG theta bursts occurred prior to generalized convulsions Heating duration: heating stopped when continuous EEG seizure discharges appeared or rectal temperature reached 45°C (3, 4)	1: [87] 2: [88] 3: [89] 4: [90]

Heated chamber (chamber in 99°C water bath)	P14	Sprague Dawley rats	In immature rats, neuronal migration disorders (NMDs) lower the threshold to HS Heating duration: 90 s, 120 s, or 150 s after T-core exceeded 42°C	[91]
Heated chamber (at 62°C)	P1, P10, or P21	Long-Evans rats	Heating duration: until a generalized convulsion was observed	[92]
Combined: chamber heated by hair dryer, within water bath	P10–P12	Rats	Single FS on P10 Heating duration: 10 min	[93]
Microwave-induced hyperthermia	P11–P17	Long-Evans rats	Hyperthermic convulsions impaired neither brain growth nor subsequent performance on behavioral tasks Heating duration: 10 min	[94,95]
Microwave-induced hyperthermia	P2–5	Chicks (epi epi)	Phenobarbital delayed onset of epileptiform seizures whereas phenytoin and valproate did not Heating duration: until moribund	[12,96]
Hot water (water jets to the head)	1: Adult P84–P98 2: P21	1: Wistar rats 2: Sprague-Dawley	Progression and EEG recording of seizure activity resemble HWE in human subjects Heating duration: 10 min at 4°C and 55°C; 20 min at 28°C, 45°C, and 50°C	1: [97] 2: [98]
Hot water (water bath)	1: P22 2, 3: P21	Sprague-Dawley rats	Novel genetic model of FS, including hyperthermia prone and resistant Heating duration: 4 min or until seizure (whichever is shorter)	1: [99] 2: [100] 3: [101]

Continued

TABLE 2 Animal models of febrile seizures, including murine, chicks, and zebrafish—cont'd

Method	Age	Species	Notes	References
Hot water model	DPF3-DPF7	Zebra fish; Wild-type and mutants	Role of heat activation of TRPV4 channels and NMDA receptor-mediated glutamatergic transmission Heating duration: 3 min	[7]
Heating pad	Adults and P15–17	Long-Evans rats	Heating duration: heated at 38.8°C or 40°C for 10 min	[102]
B. Recurrent febrile seizures				
250W infrared lamp	P5–P20	Sprague-Dawley rats	Heating duration: administered a series of HC on alternate days starting from 5 days of age to 20 days of age	[82]
500W hair dryer	P13–P15	Long-Evans rats	Heating duration: repeated hyperthermic seizures on P13 to P15	[86]
Hot water model	1: Adult 2: P20–P21	Sprague–Dawley rats	Heating duration: 4 min every 4 days (6 exposures) (1) Drug studies: 2 days/week for 2 weeks (4 exposures) (2)	1: [103] 2: [104]
Hot water model	P22	Sprague-Dawley rats	Heating duration: 1, 6, 12, 24 trials of hyperthermia exposure	[99]
Hot chamber model	P10–P12	Rats	One FS daily from P10 to P12 (three exposures) 3 × FS daily, at 4 h intervals, from P10 to P12 (nine exposures)	[93]
Hair dryer	P10–P11	Sprague-Dawley rats	Heating duration: 30 min; seizures induced two or three times at 3- to 4-h intervals	[105–108]
Hair dryer	P14, P16	Mice: (Trpv1 −/−, KO)	Heating duration: 2 × daily at P14 and P16 (4 exposures)	[77]

C. Prolonged/FSE				
Heated chamber	P8–P11	Wistar rats	Hyperthermia-induced respiratory alkalosis Long latency to seizure onset. Heating duration: 55 min (seizure duration ~25 min)	[109]
Hair dryer	P10–11	Sprague–Dawley rats	Rapid seizure onset (3–5 min), similar to humans. Reproducible seizures with EEG correlate, minimal morbidity allows long-term study Heating duration: 30 min	[22,31,33, 78,107,108, 110–121]
Hair dryer	P14–15	Mice 1: IL-1R1 –/– 2: Trpv1 –/– 3: C57/BL6l	Based on Ref. [31]	1: [105,106] 2: [77,78] 3: [34]
Temperature-regulated laminar stream of warm air (heated chamber)	1: P8–10 2, 3: P14	Mice C57BL/6J, B6(Cg)-Tyrc-2J/J, DBA/2J, AKR/J, C3H/HeJ, A/J, BALB/cByJ	Heating duration: hyperthermia maintained for 30 min	1: [22] 2: [77,78] 3: [122]
Lipopolysaccharide	P14	Sprague-Dawley rats	Intraperitoneal (IP) LPS and subconvulsive dose of KA	[32,123]
LPS and heat lamp/ hair dryer	1: P14 2: P5, 10, 15, 20	1: Long-Evans rat 2: C57Bl/6 and Cx3cr1 GFP/+ mice	Heating duration: hyperthermia maintained for 30 min 1: LPS + Hair dryer: Baram 1997 2: LPS + heat lamp: Oakley 2009	1: [124] 2: [125]

Recurrent FSs have been generated in two contexts and modalities. First, to look at "complex" seizures within a single episode. For example, in the hair-dryer model, seizures arise with hyperthermia and are typically not continuous. Thus, if the overall hyperthermia period is shorter than 30 min, the duration of the short recurrent FS is limited, recapitulating some human recurrent FS [126,127]. A second context is the generation of recurrent seizures once or several times per day, described in Table 2B [86,93,105,108].

Finally, prolonged FS and experimental FSE have been generated to examine the potential consequences of this insult on cell survival, epileptogenesis, and comorbidities of FSE-associated epilepsies. Here the goal is to provoke seizures lasting longer than 30 min, which may require hyperthermia as long as 60 min [128,129]. These models have revealed the pro-epileptogenic effects of FSE without the need for cell death and with the involvement of pro-inflammatory and epigenetic processes.

Modes and models for generating experimental FS and FSE

The goal of animal models of FS is to generate fever. However, it is practically impossible to provoke true fever in immature rodents because the fever mechanisms, residing in anterior and posterior hypothalamic neurons, are immature at this age [79]. Indeed, mice and rats are almost poikilothermic during the first days of life, so that their temperature is dependent on ambient, environmental conditions. Therefore, most immature rodent models generate hyperthermia via environmental heating.

Several distinct approaches to the generation of hyperthermia-induced seizures in animal models have been used. These include heated chambers, heated baths, streams of warm air via a hair dryer, infrared lamps, microwave, hot water, and lipopolysaccharide (Table 2).

The earliest models of FS employed an infrared lamp held above a chamber and heated until seizure activity occurred [80–83] (Table 2). During the same era (1980s), other groups employed microwaves, including 10 min in circularly polarized waveguides of a microwave [94,95]. In Japan, Morimoto's group exposed older rats (P21–25) to a hot water bath [87,89] and the group later employed heated chambers. Groups in the Netherlands employed a complex servo-regulated laminar flow chambers to induce hyperthermia, and numerous variants of providing heat, including combinations of heated chambers and water bath, have been used, as described in detail in Table 2.

Notably, the goal of any FS induction paradigm is to generate seizures in all, or the large majority of, subjects with minimal mortality and morbidity. In addition, because it is widely agreed that human FSs arise rapidly at the onset of fever and that the rate of temperature elevation might be an important contributor to FS, many groups have aimed to provoke FS rapidly [130]. In this respect, the low-cost efficient hair-dryer model of FS has gained significant popularity.

Briefly, the widely used hair-dryer model utilizes a regulated stream of moderately heated air that is directed to the top of a large 3-L glass container which serves as a hyperthermia chamber. For induction of simple or of prolonged febrile seizures, core temperatures of 39–41°C are maintained for 30 min, with core temperatures measured every 2 min. Seizures typically commence with a latency of 3–5 min and last for the duration of the hyperthermia (see below).

Other groups aim to induce fever by using bacterial endotoxin lipopolysaccharide (LPS *Escherichia coli*) and housing the rats at 30 °C. This increases temperature modestly and is followed by administration of kainic acid to induce convulsions and fever.

The variations in age, species, and duration of hyperthermia and induction to generate febrile seizures are reviewed in Table 2.

What have the models taught us? What can they not teach us?

To facilitate a greater understanding of febrile seizures, several published febrile seizure models have been developed over the past 40 years. Our discussion above has indicated the great strength of animal models to understand the mechanisms underlying the pathophysiology of febrile seizures. Genetic animal models with predisposing conditions, such as SCN1A human SMEI mutations [36–39] and GABAR mutations [70–72], have been used to mimic and provide a greater conceptual framework for clinical understanding of febrile seizures in patients with these genetic mutations. Novel tools and technologies have allowed the implication of specific genes in febrile seizure susceptibility (Tables 1A–1C) and construction of novel mouse models (Table 2). What these animal models of febrile seizures have taught us is the ability of mice with human-derived genetic epilepsies to recapitulate the clinical human phenotype. Spontaneous seizure development, reduced seizure thresholds, and greater susceptibility to hyperthermia-induced seizures have been observed in published studies of these animal models (SCN1A GEFS + R1648H, K1270T mutation, SCN9A N641Y mutation, GABAR R43Q mutation). More specifically, downstream cellular mechanisms for GABAR(R43Q), for example, as seen in both KI and KO mice and family members with this mutation, demonstrate similar reduced binding at a benzodiazepine site dependent on $GABA_A$ receptor γ2 subunit consistent with haploinsufficiency [67]. Additionally, GABAergic inhibitory interneurons in SC1A heterozygotes indicate reduced sodium currents in GABAergic inhibitory interneurons, which may cause hyperexcitability leading to epilepsy in SMEI patients [39].

Animal model studies of single and recurrent seizures in a controlled laboratory setting also allow for specifications in the context of methodological approach (infrared lamp, heated chamber, water bath, hair dryer) and timing of febrile seizure induction. These types of animal models provide valuable insight into the molecular mechanisms contributing to hyperexcitability related to prolonged febrile seizures. For example, studies have shown that HCN1, HCN2,

and HCN4 isoforms are expressed along distinct developmental trajectories in CA1 pyramidal cells of immature rat during the age when febrile seizures are provoked. The expression of these isoforms is altered by prolonged FS and FSE, promoting neuronal activity-dependent depolarization and enhanced hippocampal hyperexcitability [110,111,131–134]. These mechanisms may converge with the mechanisms by which genetic mutations of HCN channels promote early-life epilepsies [73,74,76] (see Tables 1A–1C for additional). More importantly, learning about new mechanisms from animal models allows for identification of potential therapeutic targets for preventing or reducing the pathological features of prolonged febrile seizures and epilepsy.

While these animal models may be important and suitable for answering certain questions, there are other questions that may not be completely addressed. For example, in many febrile seizure models, seizures are induced by hyperthermia and not by fever, which may implicate alternative mechanisms. Parsing out the complexity of genetic heterogeneity and understanding the relative contribution of all genetic factors to the consequence of febrile seizures will consistently prove an important hurdle to remember in the laboratory, but there remains no better answer to study the intricacies of febrile seizures and their consequences for children.

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