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CHAPTER

26

Complex Febrile Seizures—An Experimental Model in Immature Rodents

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This chapter describes a rodent (rat and mouse) model of prolonged febrile seizures. Study of these seizures is important, because they are common, illustrative of seizures—and of abnormal excitability—in the immature brain, and associated with subsequent epilepsy. Seizures generated in this model are evoked by hyperthermia, via mechanisms common to those of fever. The seizures are limbic in semiology and involve the hippocampal formation. When sustained for ~20 minutes, these experimental complex febrile seizures result in transient neuronal injury but no cell death. The seizures induce enduring structural, molecular, and functional changes in the hippocampal formation, including altered expression of the hyperpolarization-activated cyclic nucleotide gated cation (HCN) channels. Threshold temperature for evoking the seizures provides a ready measure of excitability that is suitable for pharmaceutical screens, as well as for screening for the effects of genetic mutations/gene engineering on seizure susceptibility.

GENERAL DESCRIPTION OF THE MODEL: WHAT DOES IT MODEL?

The model described here recapitulates the essential elements of prolonged febrile seizures in the human. Febrile seizures are the most common type of seizures in infants and young children, with a prevalence of 2–14% around the world (see Stafstrom, 2002 for a recent review). For short or simple febrile seizures, epidemiologic and prospective studies as well as retrospective analyses have suggested that seizures with duration of less than 10 (Annegers et al., 1987; Berg et al., 1997) or 15 minutes (Nelson and Ellenberg, 1978) do not lead to long-term sequelae. Thus, neither epilepsy nor cognitive dysfunction are described in children with a limited number of short febrile seizures (Verity et al., 1985, 1998; Berg and Shinnar, 1996a). However, complex febrile seizures, defined as prolonged, having focal features, or that recur within a single febrile episode, are more controversial (Annegers et al., 1987; Berg and Shinnar, 1996b). Whereas there is limited epidemiologic evidence for adverse outcome, retrospective analyses strongly link a history of prolonged febrile seizures to temporal lobe epilepsy (TLE) (Cendes et al., 1993; French et al., 1993; Hamati-Haddad and Abou-Khalil, 1998; Theodore et al., 1999).

The controversy over the clinical outcome of prolonged febrile seizures, and the potential that they may promote epileptogenesis, provides a strong impetus for modeling them. Animal models, unlike the human condition, allow direct investigation of the potential consequences of these seizures. Hypotheses about mechanisms by which febrile seizures might influence the developing brain can be formulated and tested directly, using diverse neuroanatomic, molecular, electrophysiologic, and imaging methods.

A second impetus for developing a model of febrile seizures is to understand the mechanisms by which they are generated. Even if not causing epilepsy, febrile seizures are common, frightening, and associated with iatrogenic complications from treatment; their prevention requires an understanding of how they arise. Thirdly, febrile seizures constitute a common manifestation of hyperexcitability in the developing human brain. Because they do not occur in adults, they provide an excellent tool for studying the unique characteristics (and underlying mechanisms) of abnormal excitability during development. In addition, as a generalizable model of developmental hyperexcitability,

experimental febrile seizures provide a useful model for screening potential anticonvulsants for developmental epilepsies. Finally, genes that may lead to increased excitability might render the developing animal more susceptible to developing febrile seizures: the model provides a valuable instrument for screening epilepsy- or seizure-promoting genes.

The model described here is suitable for investigating the five types of questions mentioned above. This chapter discusses the generation of either short or prolonged experimental febrile seizures in the immature rat, as well as adaptation of the model to the immature mouse, where it can be coupled to the power of mouse genetics.

METHODS OF GENERATION OF EXPERIMENTAL PROLONGED FEBRILE SEIZURES

Procedural Issues: Animal Species and Age, Controls, Fever Versus Hyperthermia

Species

A model of experimental prolonged febrile seizures was first developed in the immature rat (Baram et al., 1997; Toth et al., 1998, Dubé et al., 2000) then adapted successfully to several strains of mice (Dubé et al., 2005a).

Age

In the human, febrile seizures occur between ~3 months and ~5 years of age with a peak incidence at 18 months (Nelson and Ellenberg, 1981; Hauser, 1994). Comparing the development of the hippocampal formation between humans and rodents indicates that the first year of human life may be equivalent to postnatal days 7–14 (P7–14) in the rat (Table in Avishai-Eliner et al., 2002). Therefore, an appropriate rat model of febrile seizures should use rats at a developmental stage at which human infants are most susceptible to febrile seizures. In addition, systematic analysis of the temperatures required to elicit hyperthermic seizures shows that this susceptibility is age-dependent, with a nadir of threshold temperature during the second week of life (Olson et al., 1984; Hjeresen and Diaz, 1988; Morimoto et al., 1990, 1991; Baram et al., 1997). We have elicited experimental febrile seizures in P6–17 rats and in P11–17 mice and have chosen to use P10–11 for rat and P14–15 in mouse for three reasons: (1) Consideration of hippocampal development (see preceding); (2) these ages fall at the nadir of threshold temperature, and, remarkably, these threshold temperatures are close to those required in normal children (Berg et al., 1992); and (3) the behavioral seizures at these ages are reliable, reproducible, and stereotyped.

Controls

Induction of seizures using hyperthermia involves two variables: (1) hyperthermia and (2) hyperthermia-induced seizures. Therefore, to ascertain that any consequence of hyperthermic seizures is truly a result of the seizures rather than of the hyperthermia *per se*, hyperthermic controls must be used. These are generated by subjecting age-matched littermates to the same degree and duration of hyperthermia but preventing seizures using short-acting barbiturates (pentobarbital intraperitoneally; Dubé et al., 2000; Brewster et al., 2002).

Fever Versus Hyperthermia

Febrile seizures in humans are convulsions associated with fever. The model described here relies on hyperthermia rather than fever to evoke seizures. We think this is justified for three reasons: (1) Hyperthermia without fever also causes seizures in infants (in the setting of anticholinergics or theophylline overdose or hot water baths); (2) it is almost impossible to provoke true fever (>1°C increase of core or brain temperature) in infant rats (Heida et al., 2003). Importantly, fever and hyperthermia may utilize common mechanisms to elicit seizures: The pyrogenic cytokine IL-1 contributes to fever generation and, conversely, fever leads to IL-1 production within hippocampus (Takao et al., 1990; Ban et al., 1991; Cartmell et al., 1999; Gatti et al., 2002). These facts support the involvement of IL-1 in the mechanisms of both febrile and hyperthermic seizures. Others (Blake et al., 1994; Haveman et al., 1996) and our data (Dubé et al., 2005a) demonstrate that release and synthesis of IL-1 are governed primarily by the actual increase of temperature (hyperthermia) rather than other components of the febrile response. Thus, mechanisms by which fever and hyperthermia induce seizures may be similar, sharing cytokines as a key mediator (Rothwell and Luheshi, 1994, 2000; Gatti et al., 2002; Dubé et al., 2005a).

Procedures

General Procedure

Experimental prolonged febrile seizures are induced in 1–2 rats or mice at a time. Features of the paradigm that are common to both species will be discussed, followed by points that distinguish each specie. Procedures for EEG recordings will be found in the Monitoring section, following. Experiments are initiated at 8–11AM to minimize potential diurnal variability in seizure susceptibility. Pups are placed on a euthermic pad at least 15 minutes before the onset of hyperthermia. Baseline core (rectal) temperature is measured using a hypodermic needle probe (HYP2-21-1-1/2-TG-48-OSTM, Omega, Stamford, CT) connected to a temperature indicator (DP41-TC, Omega Stamford, CT). To

prevent variability of baseline core temperature, pups are prevented from climbing on top of one another. Two pups are placed in a 3-liter jar (the hyperthermia chamber) fitted with a cloth pad taped to its bottom, to absorb excreta and prevent exposure to heated glass. The chamber is covered by a styrofoam lid with a central hole and placed in a Faraday cage. After measuring onset core temperatures, a regulated stream of moderately heated air is blown obliquely through the hole in the lid using a commercial adjustable hair dryer (Prostyler 1600W, 097RIR, Conair, set at medium). The goal is to increase core and brain temperatures ~2° C/minute until seizure onset, when seizure temperature threshold is measured. Times of hyperthermia onset and seizure onset are noted. In our hands, increasing the temperature at ~2° C/minute leads to a latency of 2–4 minutes and an excellent correlation of brain and core temperatures.

Prolonged Experimental Febrile Seizure Protocol

These are generated by maintaining hyperthermia (40–42° C) for 30 minutes, with seizure onset considered time 0. Once seizures commence, hyperthermia is continued, and the temperature measured every 2 minutes. If core temperature is >41.5° C, pups are removed to a cool metal surface for 2 minutes to prevent excessive heating. The cycle of warming for 2 minutes, temperature measure, and continued warming or time-out is maintained for a total of 30 minutes, resulting in seizures of ~24.1 minute (Table 1). The procedure yields seizure threshold temperatures of ~40.8° C and mean duration of hyperthermia of ~27.9 minute.

Recovery Procedure

Following hyperthermia pups are submerged (1 second) in room temperature water, hydrated orally (~0.1 ml water) using a 1 cc syringe, and transferred to a cool metal surface until their core temperature reaches 32–34° C. They are kept on a euthermic pad for 1 hour then returned to home cages. In our hands, rat and mouse dams receive the pups without difficulty and initiate grooming and nursing. We keep total separation time from the dams to less than 4 hours, and have observed no weight loss or growth retardation after the procedure.

Monitoring

Temperature

Human febrile seizures are typically elicited by temperatures higher than 38.5° C, and a study in Swedish children suggested a normal threshold temperature of 40.9° C (Knudsen, 1996). In addition, brain temperatures higher than 43° C may provoke neuronal injury (Burger and Fuhrman, 1964; Germano et al., 1996). Therefore, this model limits maximal temperatures to ~42° C, and importantly correlates the measured (core) temperature to that of brain.

While the goal of the monitoring is to maintain core and brain temperatures in the 40–42° C range, it is not feasible to monitor brain temperature chronically in P10 rats (or P14 mice) because of the size of available implantable probes. Therefore, we have correlated brain and core temperatures in the model, under standard conditions of the velocity and temperature of the heating air stream (see following text). This is important, because core temperature may rise disproportionately to that of brain. Figure 1 shows a series of measurements of core- and brain-temperatures in individual rats. Baseline core values were measured at 5-minute intervals over a 25-minute period, and averaged 32.88 ± 0.07°C (n = 10) (Figure 1A). These temperatures were virtually identical to those obtained in rats upon removal from home cages (not shown). Under the same conditions, brain temperatures for an individual rat were also highly consistent (Figure 1B). Interestingly, mean euthermic (normal) brain temperatures were 2.8° C higher than mean core values. This divergence was temperature-dependent and approached zero at temperature ranges provoking seizures. Thus, at the onset of experimental prolonged febrile seizures (i.e., at threshold temperatures), brain temperatures averaged 40.7 ± 0.2° C (n = 29) and core temperatures were 40.88 ± 0.3° C (n = 31; Dubé et al., 2005b). These data indicate that, within the confines of the parameters recommended for this model, core measurements provide an adequate approximation of brain threshold temperatures for experimental febrile seizures. It is recommended that each laboratory perform initial experiments correlating brain and core temperatures under the conditions it uses.

EEG Monitoring

EEG monitoring is performed whenever the model is being set-up, then periodically and when a new species or

TABLE 1 Parameters of Seizures and of Hyperthermia in the Immature Rat Febrile Seizures Model

Group parameters	n	Maximal Temperature (°C)	Threshold temperature (°C)	Hyperthermia duration (min)	Seizure duration (min)
Experimental febrile seizures	209	42.5 ± 0.02	40.8 ± 0.06	27.9 ± 0.07	24.1 ± 0.1
Hyperthermic controls	26	42.3 ± 0.047	—	28.4 ± 0.23	—

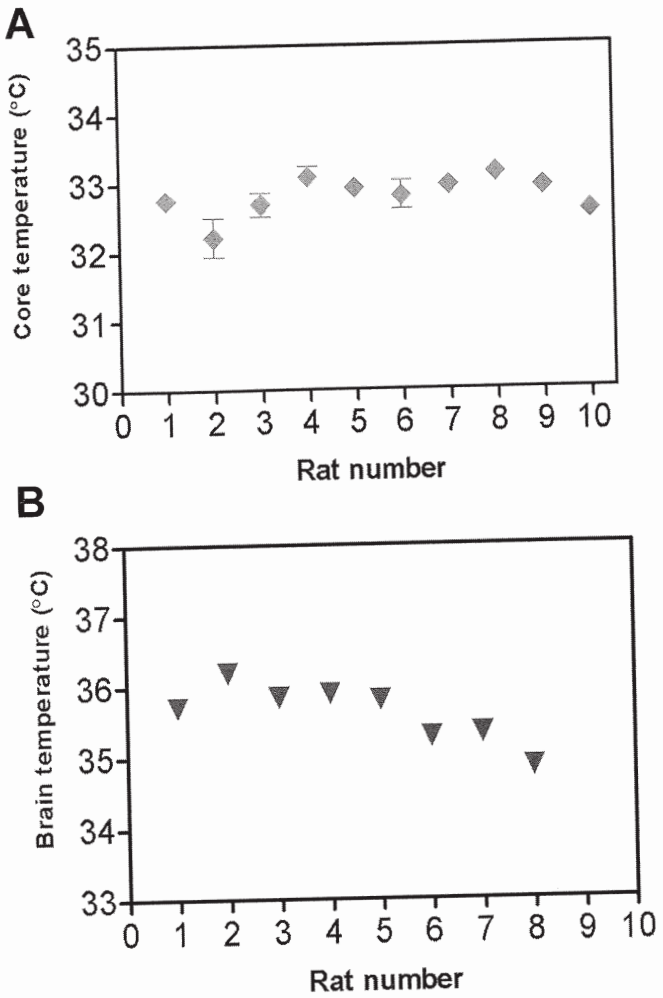

FIGURE 1 Correlation of brain and core temperatures in the euthermic immature rat. **A**: Core temperatures of individual rats are tightly clustered within and among individuals. Diamonds denote means ± standard errors of five measurements obtained over 25 minutes from individual rats kept on a euthermic pad. (Values for rat #1 were too clustered to visualize error bars.) **B**: Brain temperatures, obtained under the same conditions by directing the probe through the cranial suture to the dura. These temperatures were on average 2.8° C higher than core ones (modified from Dubé et al., 2005b, with permission).

mouse strain is added. Methods for implanting electrodes in limbic structures of immature rodents have been published (Baram et al., 1992; Dubé et al., 2000, 2005a). See EEG features of the seizures in the section following.

Behavior

Behavior is determined for each 2-minute epoch within the 30 minutes of hyperthermia. The characteristic behaviors for mice and rats are described in Behavioral Features, following.

Recovery

Sedation in the hyperthermic control groups persists typically for ~1 hour; these rats are hydrated orally and handled as described in the preceding for the other groups: Following hyperthermia, pups are removed to a euthermic pad and hydrated. They are returned to home cages when fully awake and recovered. Little evidence of dehydration is found in the hyperthermic control and experimental prolonged febrile seizures groups (<3% loss of body weight).

Ease of development and reliability are discussed in the limitations section (IV).

Occurrence of Spontaneous Seizures

Whereas we have previously published on the absence of spontaneous seizures in this model, these observations were based on daytime intermittent observation and EEG recording (Dubé et al., 2000). Using nocturnal simultaneous video-EEG recordings, there is preliminary evidence for the occurrence of spontaneous seizures (epilepsy) in a subgroup of the rats that had sustained experimental febrile seizures. These studies are ongoing.

CHARACTERISTICS/DEFINING FEATURES

Behavioral Features

The initial seizure behaviors in both immature rats and mice consist of *acute sudden* arrest of the hyperthermia-evoked running and other types of hyperactivity. Freezing (altered consciousness?) is seen in both species, followed rapidly by oral automatisms. This sequence at seizure onset is typical for human and animal seizures of limbic origin. The subsequent course of the seizures differs somewhat between immature rats and mice.

In rats, freezing (Racine stage 0) is followed by oral automatisms (chewing/biting, Racine stage 1) and often forelimb clonic movements (Racine stage 3) (Racine, 1972). A typical behavior, which can be used for consistent recording of threshold temperature, is the sudden chewing/biting of an extremity. Later in the seizures, tonic body flexion may occur and may indicate an eventual propagation of the seizure to the brainstem.

In mice, onset of experimental febrile seizures (when seizure threshold temperature is measured) is heralded by sudden immobility, with reduced response to stimulation (altered consciousness), and often with facial automatisms (chewing, vibrissae movements). Tonic body flexion is not observed in mice.

Electrographic Seizures

During development of the model, to investigate the epileptic nature of the behavioral seizures provoked by

hyperthermia and determine their origin and location within the brain, electrophysiologic recordings from multiple brain sites have been conducted in rats and mice. As mentioned above, initial seizure behaviors in both species consist of acute sudden cessation of hyperthermia-evoked hyperactivity, with freezing and oral automatisms, a typically limbic behavior. Indeed, bipolar electrode recordings from basal amygdala, dorsal hippocampus, and frontoparietal cortex of freely moving pups (Baram et al., 1992, 1997; Dubé et al., 2000) suggested the onset of EEG spike-trains in hippocampus and amygdala that coincided with the immobility and oral automatisms, with no change or flattening of cortical EEG activity. The ictal EEG activities during experimental febrile seizures in the P10–11 rat have been published (Dubé et al., 2000; Brewster et al., 2002). They consist of trains of spikes and spike-waves with progressively increasing amplitude in hippocampal and amygdala leads, with variable progression to the cortex. The EEG patterns in the mouse are quite similar and are shown below (Figure 2).

Neuropathology

In mature hippocampus, seizure-induced alteration of brain excitability and development of TLE are generally believed to require death of specific populations of hippocampal neurons (Houser, 1999).

Experimental prolonged febrile seizures in immature rodent lead neither to acute neuronal death, as determined using the *in situ* end labeling technique (Toth et al., 1998), nor to long-term neuronal death, evaluated up to 3 months after the seizures (Bender et al., 2003a). This neuronal sparing includes populations that have been shown to be the most vulnerable to seizures-induced cell death in adult models of limbic seizures, including specific subpopulations of interneurons (Houser and Esclapez, 1996; Buckmaster and Dudek, 1997) and mossy cells (Sloviter, 1994). However, experimental prolonged febrile seizures induce transient neuronal injury in limbic structures including hippocampus, amygdala, and perirhinal cortex, visualized using silver staining (Toth et al., 1998), but not Fluoro-Jade (Dubé et al., 2004). The distribution of argyrophilic neuronal injury observed in this model overlaps the structures involved in TLE, including hippocampal pyramidal cells, lateral basal and central nuclei of amygdala, and the perirhinal cortex, and persists up to 2 weeks. Because argyrophilia (but not Fluoro-Jade) targets cytoskeletal proteins, the results using these two methods implicate these proteins in the transient changes evoked by experimental febrile seizures.

Among other potential structural processes that may be provoked by seizures and may contribute to the epileptogenic process, prolonged febrile seizures do not modify granule cell neurogenesis in the immature hippocampal

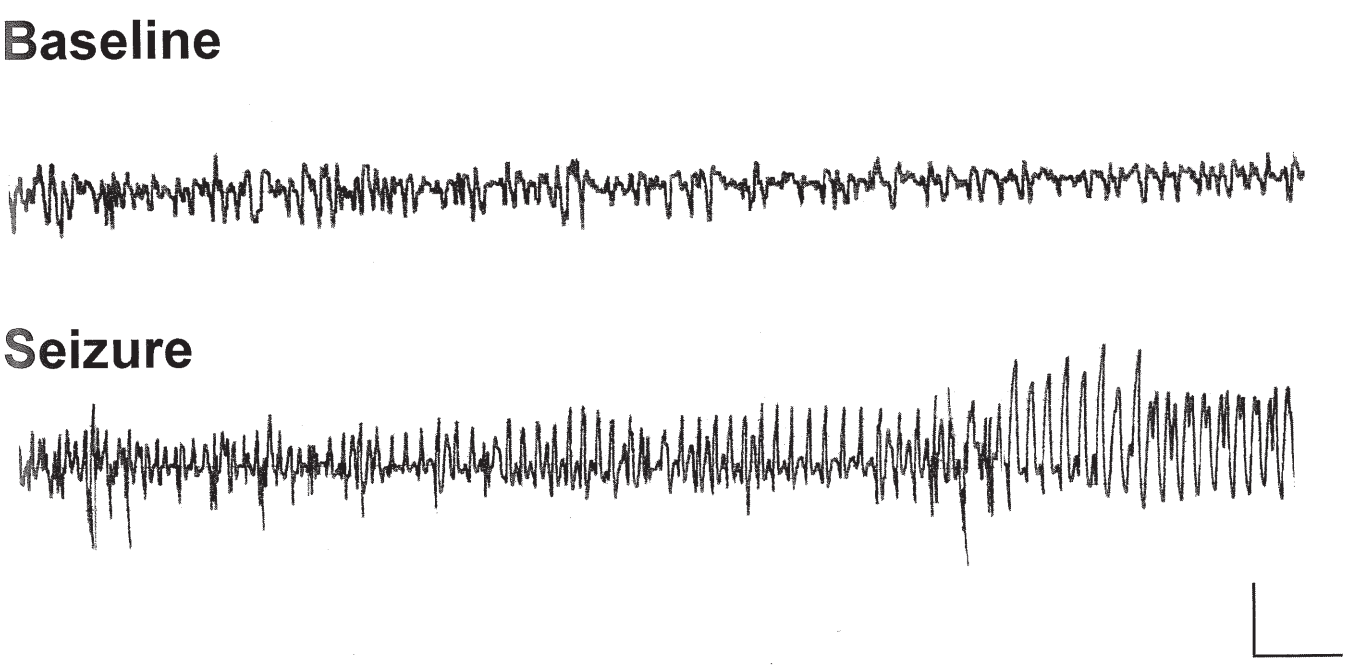

FIGURE 2 Hippocampal EEG recordings from immature mouse (P14): Low amplitude baseline trace with variable rhythms is replaced by epileptiform discharges (trains of spikes and spike-and-waves) evoked by hyperthermia. The behavioral correlates of the EEG seizure consist of sudden behavioral arrest associated with facial limbic automatisms. Calibration: vertical, 50 μV; horizontal, 2 seconds.

formation (Bender et al., 2003a). Similarly, sprouting is not prominent after these seizures (Bender et al., 2003a).

Imaging

Using serial magnetic resonance imaging (MRI) on a 4 Tesla scanner, prolonged experimental febrile seizures were found to increase T2 signal in limbic structures in 75% of animals at 24 hours and in 87.5% of the seizure group a week later. These involved dorsal hippocampus, amygdala, piriform cortex and the medial ventroposterior thalamic nucleus (Dubé et al., 2004). The T2 signal changes were not accompanied by evidence of neuronal injury or death in these regions (assessed using Fluoro-Jade), but may indicate other cellular pathologic processes that promote epileptogenesis.

Molecular Changes

Seizure-evoked hippocampal hyperexcitability was apparent by a week after the seizures and persisted long term (Dubé et al., 2000; Chen et al., 1999, 2001), indicating the occurrence of profound molecular changes. The spectrum and sequence of molecular changes evoked by experimental prolonged febrile seizures in this model have not yet been fully explored. In addition, the molecular events that have already been elucidated are complex and fall outside the scope of this chapter. The interested reader is referred to: Toth et al., 1998; Chen et al., 1999, 2001; Brewster et al., 2002, 2004; Bender et al., 2003a, b; Santoro and Baram, 2003; Dubé et al., 2005a. Briefly, within hours after seizures, regulation of calcium (Ca^{2+}) entry was altered as a consequence of transient down-regulation of GluR2 expression and the formation of Ca^{2+}-permeable AMPA receptors (Pellegrini-Giampietro et al., 1997; Eghbal-Ahmadi et al., 2001) that also permitted Zn^{2+} accumulation in CA3 neurons (Yin et al., 2002). Perhaps as a consequence of these events, the transcription of other specific channels was altered, starting already by 24–48 hours (Brewster et al., unpublished): The mRNA levels of the hyperpolarization-activated cyclic nucleotide-gated cation channel type 1 were reduced, whereas HCN2 channel gene expression was enhanced (Brewster et al., 2002). These mRNA levels were followed by a "molecular switch" of HCN1/HCN2 ratios also at the protein level (Brewster et al., 2005), and should promote hyperpolarization-evoked rebound neuronal firing (Chen et al., 2001; Santoro and Baram, 2003), i.e., enhanced hippocampal excitability.

It is notable that expression of HCN channels is altered also in the "sclerosed" hippocampus of humans with severe TLE (and typically a history of early life seizures; Bender et al., 2003b). These expression changes, consisting of *increased* HCN1, may potentially be neuroprotective (Bender et al., 2003b; Santoro and Baram, 2003).

Response to Antiepileptic Drugs/Usefulness in Screening Drugs

In human febrile seizures, phenobarbital, valproate, and the benzodiazepines are effective in controlling febrile seizures while other anticonvulsants including phenytoin and carbamazepine are ineffective (e.g., Knudsen, 2002). This anticonvulsant efficacy profile is recapitulated in the model of febrile seizures (Dubé and Baram, unpublished data). Therefore, the model should be useful for screening pharmaceutical agents as potential anticonvulsants in the developing brain.

Genetic Influence

Using this model, febrile seizures have been generated in rats and several strains of mice. Seizures are evoked in virtually all immature rodents (P10–11 rat; P14–15 mice) regardless of genetic background. However, genetic background affects the threshold temperatures for eliciting the seizures: temperatures resulting in seizures in, e.g., C57BL mice ($39.7 \pm 0.3°C$, $n = 17$) are significantly lower than those in mice of the 129/Sv strain ($41.3 \pm 0.2°C$, $n = 21$; Dubé et al., 2005a); furthermore, genetic manipulation of the interleukin 1 gene receptor led to significant elevation in threshold temperature, implicating this gene in the mechanisms of febrile seizure generation (Dubé et al., 2005a). Therefore, the model is suitable for testing the effects of gene(s) of interest on neuronal excitability and seizure susceptibility in the developing brain.

LIMITATIONS

As implied in the previous paragraphs, the setup of this model simply does not require costly equipment. However, it does require certain procedures in each laboratory to validate the nature of the evoked seizures, the absence of hyperthermia-induced injury, and the correlation of brain and core temperatures:

1. Because routine monitoring involves only core temperature, maintaining consistent conditions after verifying the correlation of core and brain temperatures is important. This involves using the same hair dryer with the same setting, held at a constant distance and angle. Rigorous training of personnel and periodic correlation of core and brain temperatures are recommended.
2. To avoid direct hyperthermic injury and agonal, terminal seizures, temperatures should be carefully controlled and maintained at 40–42° C. Specifically, those higher than 43° C may lead to direct injury. As an additional requirement, a hyperthermic control group (with hyperthermia but without seizures, achieved by barbiturate pre-admin-

istration) is required in studies assessing the effects of the seizures.

3. Mice have a somewhat wider spectrum of seizure behaviors. In addition, genetic background has a profound effect on susceptibility to these seizures (see preceding section, Genetic influence). Therefore, attention to controls of appropriate genetic background when assessing the consequence of any gene alteration is necessary.

While mortality rate is nil, prevention of morbidity requires maintaining distance from the source of heated air, avoiding excessive temperatures, and using padded hyperthermia chambers. These precautions, as well as rinsing the chamber with room temperature water between rounds, eliminate burns, particularly of the paws.

Reproducibility

This model of prolonged febrile seizures is highly reproducible. In our hands more than 99% of the rats develop prolonged seizures, and threshold temperatures in over 500 rats have been in a narrow range. In addition, to our knowledge at least a dozen laboratories around the world have applied the model to both rats and mice.

Because this is not an extreme model (in comparison, for example, to status epilepticus, that kills 100% of a given neuronal population), a degree of interanimal variability is unavoidable (Brewster et al., 2002; Bender et al., 2003a; Dubé et al., 2005a). The molecular, structural, and imaging changes are evident in >87.5% (MRI; Dubé et al., 2004)—>90% (HCN channel changes) of rats, but not in 100%. Therefore, size of experimental groups (n) larger than 6 is recommended.

INSIGHTS INTO HUMAN DISORDERS

This model provides insight into febrile seizures and their mechanisms as well as their potential consequences. It provides a model of epileptogenesis in the developing brain with molecular, physiologic, and functional changes, as well as the onset of spontaneous ones (epilepsy). In addition, it provides a screen for manipulations aiming to modify excitability (seizure susceptibility) in the developing brain, be they genetic or pharmaceutical.

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Models of SEIZURES AND EPILEPSY

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