

RESPIRATORY ALKALOSIS: “BASIC” MECHANISM OF FEBRILE SEIZURES?

Experimental Febrile Seizures Are Precipitated by a Hyperthermia-Induced Respiratory Alkalosis. Schuchmann S, Schmitz D, Rivera C, Vanhatalo S, Salmen B, Mackie K, Sipila ST, Voipio J, Kaila K. *Nat Med* 2006;12:817–823. Febrile seizures are frequent during early childhood, and prolonged (complex) febrile seizures are associated with an increased susceptibility to temporal lobe epilepsy. The pathophysiological consequences of febrile seizures have been extensively studied in rat pups exposed to hyperthermia. The mechanisms that trigger these seizures are unknown, however. A rise in brain pH is known to enhance neuronal excitability. Here we show that hyperthermia causes respiratory alkalosis in the immature brain, with a threshold of 0.2–0.3 pH units for seizure induction. Suppressing alkalosis with 5% ambient CO₂ abolished seizures within 20 s. CO₂ also prevented two long-term effects of hyperthermic seizures in the hippocampus: the upregulation of the I_h current and the upregulation of CB1 receptor expression. The effects of hyperthermia were closely mimicked by intraperitoneal injection of bicarbonate. Our work indicates a mechanism for triggering hyperthermic seizures and suggests new strategies in the research and therapy of fever-related epileptic syndromes.

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COMMENTARY

Fever represents a typical response to infection at all ages. However, only in young children is prolonged fever capable of inducing convulsions. While febrile seizures are generally considered benign, there is emerging evidence that in certain cases they can lead to chronic epilepsy. Several factors, such as altered phenotype of hyperpolarization-activated cyclic nucleotide-gated channels, altered hyperpolarization-activated cation current (I_h), enhanced endocannabinoid signaling, and mossy fiber sprouting, have been implicated in the mechanisms of increased neuronal excitability and of epilepsy following febrile seizures (1–3). However, in order to prevent long-term pathophysiological sequelae, it is important to understand the basic mechanisms that trigger febrile seizures per se and why febrile seizures usually only occur in pediatric population.

Because fever is commonly associated with inflammation, inflammatory cytokines have been regarded as candidate mechanistic factors of febrile convulsions. However, data accumulated to date do not provide compelling evidence that inflammatory cytokines are directly involved in the development of febrile seizures. Thus, while some reports link interleukin-1 β (IL-1 β) gene polymorphisms with febrile seizures (4), other studies did not find any association between the two phenomena (5). A study using IL-1 β receptor deficient mice proved that IL-1 β , a key inflammatory cytokine, was not required for febrile seizures to occur, although it could have a modulatory effect (6). Furthermore, inflammatory cytokines are expressed both in adult and in immature brain and have been shown to regulate adult epileptogenesis (7); thus, inflammatory cytokines alone cannot explain age specificity or, consequently, the mechanisms of febrile convulsions.

Two features of febrile seizures—rapid onset and age selectivity—suggest that certain highly reactive mechanisms specific for the immature age are responsible for their occurrence and progression. Schuchmann and colleagues focused their study on the examination of these mechanisms. The authors exploited the well-established fact that fever is commonly accompanied by compensatory hyperventilation, which in turn might lead to an alkaline shift in pH as a result of a decrease in the partial pressure of CO₂. At the same time, elevated brain pH is known to enhance neuronal excitability.

Schuchmann and coworkers performed a series of elegant experiments designed to connect the dots and identify mechanisms that may underlie the occurrence of febrile seizures. They compared behavioral, electrographic, physiologic, and chemical responses to hyperthermia induced in immature rats of two ages: 8–11 days, when seizures readily develop in response to the elevating of core temperature, and 3 weeks, when the increase in body temperature does not result in seizure responses. Their major findings were that (a) hyperthermia led to a 60% increase in breathing rate in younger rats, whereas in 3-

week-old animals, a similar rise in body temperature increased breathing rate by 28%; (b) in younger animals, hyperventilation was accompanied by a 3% increase in brain pH, while at 3 weeks pH increase was 0.5%; (c) as expected, younger but not older rats developed seizures in response to hyperthermia. These observations were followed by simple, yet impressive, experiments. The authors showed that by directly elevating pH to the same level as induced by hyperthermia (using systemic injection of bicarbonate), behavioral and EEG seizures could be readily induced in 8- to 11-day-old rats. However, they did not examine whether a similar injection of bicarbonate to 3-week-old animals would have failed to induce alkalinization and seizures; such an experiment would have further validated their hypothesis.

One logical conclusion and practical implication of the findings of Schuchmann and coworkers is that normalizing partial pressure of CO₂ may be effective in blocking febrile convulsions in rat pups. Indeed, the authors found that the application of 5% CO₂ to the inhaled air completely blocked electrographic and behavioral manifestations of febrile convulsions. Even more remarkably, long-term consequences of febrile seizures, such as upregulation of I_h current and overexpression of cannabinoid receptors, were prevented by the CO₂ therapy. Although the authors did not explore whether such treatment also blocked long-term enhanced excitability and predisposition to seizures (which would make their findings even more exciting), they showed that apparent substrates of postfebrile seizure-induced epileptogenesis were blocked.

The question of why younger animals, compared to older animals, developed more profound hyperventilation that was sufficient to raise pH to the seizure-inducing level was not directly addressed in the experiments. However, it has been established that the lowest ontogenic chemosensitivity to CO₂ occurs in rats around postnatal day 10, which is precisely when febrile seizures occur. Hence, central feedback mechanisms that control respiratory rate based on the partial pressure of CO₂ are not mature in younger animals. The inability to keep CO₂ concentration within physiological parameters might eventually lead to tissue alkalinization and ultimately to seizures.

The importance of these studies also might extend beyond an understanding of the mechanisms of febrile seizures. While respiratory alkalosis appears to be age- and model specific, it is quite possible that shifts in brain pH, in general, could play an important role at various ages and in other types of epilepsy. Accordingly, it has been shown that a focal increase in pH in chronic epileptic adult animals is associated with the generation of spontaneous interictal spikes and could contribute to the interictal–ictal transition (8). Therefore, when superimposed on chronically modified neuronal circuits in the epileptic

brain, the momentary alkalization that occurs as a result of normal variations in pH might be a mechanism by which individual seizures are triggered in epileptic patients. In this regard, hyperventilation is long known to induce interictal spikes and is commonly used for the EEG diagnosis of epilepsy. Furthermore, carbonic anhydrase inhibitors, such as acetazolamide, are known to exert anticonvulsant effects (9). Clearly, the findings of Schuchmann and colleagues offer important basic and translational implications. If proven true in the clinical environment, these data could provide a simple, safe, and effective treatment for febrile seizures in infants, with both immediate and long-term benefits.

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