Slow and fast kindling during hyperthermic stimulation in rats: Implications for hot water epilepsy

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Abstract

Hot water epilepsy, a reflex epilepsy precipitated by hot water stimulation, has been commonly reported from southern India. Clinical studies have indicated that a phenomenon of hyperthermic kindling may underlie the appearance of spontaneous seizures in some hot water epilepsy patients at a later stage. Our present experiments with a rat model for hot water epilepsy demonstrate the occurrence of slow and fast kindling during hyperthermic seizures, induced by repeated stimulations with hot water, in different populations of rats. These findings have important implications for the pathophysiology and management of this epileptic syndrome in human beings.

Key words: Hot water epilepsy, hyperthermic kindling, hyperthermic seizure, kindling rate.

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Introduction

Hot water epilepsy (HWE) is a reflex stimulus-sensitive epilepsy in humans, most commonly reported from southern India (1, 2). It is usually precipitated by the pouring of hot water over the head, and clinically manifests itself in the form of complex partial or generalised tonic-clonic seizures (1, 2). Studies at the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, have shown that these seizures eventually become spontaneous in 25 % of the patients, suggesting a phenomenon of "hyperthermic" kindling (3). A question that arises here is whether the remaining 75 % of the patients fail to kindle at all, or whether they are slow kindlers.

In order to understand this phenomenon further and based on our clinical experience, we developed an animal model for HWE in rats by pouring hot water at 53°C over their heads, simulating the pouring of hot water in humans (4). Interestingly, we were able to demonstrate the occurrence of kindling in these animals by such repeated hyperthermic stimulations. In this paper, we further report a phenomenon of fast and slow kindling in our experimental animals. The expression of these two processes should ultimately enable us to develop inbred lines of seizure-prone (fast kindling) and relatively seizure-resistant (slow kindling) rats for further characterisation of the syndrome.

Methods

Fifty male Wistar albino rats, 12-16 weeks old (150-200g) were obtained from two registered sources: the National Institute of Nutrition, Hyderabad (Source A), and the National Centre for Biological Sciences, Bangalore (Source B). The rats were housed individually under standard laboratory conditions – 25°C, 50 % relative humidity, 12 h/12 h light and dark cycles, with free access to food and water. The experiments were initiated after a week of habituating the animals to the laboratory conditions.

The rats were singly placed in a plastic chamber of dimensions 40 x 50 x 15 cm. Hot water at 53°C was then delivered on the head of each rat with a 10 ml tumbler (4). The animals were freely ambulant in the chamber during the stimulation. The chamber had a fine mesh at the base for the continuous drainage of water. The end point of stimulation was either the initiation of a seizure or 5 min of stimulation. The animals were next cooled under running tap water (ambient temperature) for 2 min. They were then gently dried with a soft towel and returned to their home cages.

Stimulations were repeated every 48 h. During each stimulation, the latency, duration, and the grades of seizures attained were recorded. Klauenberg's method of grading was employed (5). Attainment of grade 5 in the animal was assumed to indicate

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a kindled state, wherein a generalised seizure was observed. The number of stimulations required by each animal for kindling was also noted. All the experiments were examined and cleared by the Animal Ethics Committee of the M.S. Ramaiah Medical College, Bangalore. The statistical analysis of the data employed non-parametric methods, including the Mann-Whitney U-test and the Kolmogorov-Smirnov two-sample test (6).

Results

All the 50 rats developed seizures on hyperthermic stimulation. The number of stimulations required for kindling, or the kindling rate, demonstrated a bimodal distribution for the experimental population with two distinct peaks (Figure 1). The gradual tapering down of both these peaks at each end indicated that this population of rats could consist of two subpopulations differing in their kindling rates. A source-wise analysis of the experimental rats from the two different sources did, in fact, yield significantly different distribution patterns of kindling rate (Figure 2; Kolmogorov-Smirnov two-sample test; $n = 33, 17$; $D = 0.463$, $p < 0.05$). The mean ($\pm$ SD) kindling rates for the rats from Sources A and B were 8.9 ($\pm$ 4.2) and 4.7 ($\pm$ 2.3), respectively; these rates were also significantly different from each other (Mann-Whitney U-test; $n = 33, 17$; $p < 0.01$). Since all the experimental rats were both age- and weight-matched, the two subpopulations could represent a possible population genetic difference in the susceptibility of these rats to hyperthermic kindling.

Discussion

Kindling refers to a progressive increase in neuronal activity, usually in areas associated with the forebrain, on repeated stimulation (7). The occurrence of kindling in human brains, however, has generally been debated (8). In our clinical experience with HWE, we had earlier observed that about 25 % of the patients developed progressive seizures that eventually became spontaneous, suggesting a possible involvement of hyperthermic kindling.

Our present results clearly demonstrate the presence of slow and fast kindling in the ontogeny of hyperthermic seizures in rats. In the light of this finding, the possibility of a similar phenomenon underlying the appearance of spontaneous seizures in some HWE patients must be considered seriously. If an involvement of a process of kindling can indeed be confirmed, the other class of patients who do not exhibit such seizures at a corresponding stage must be followed up to detect the possible appearance of spontaneous seizures at a later stage.

The occurrence of slow and fast hyperthermic kindling in age - and weight-matched rats suggests

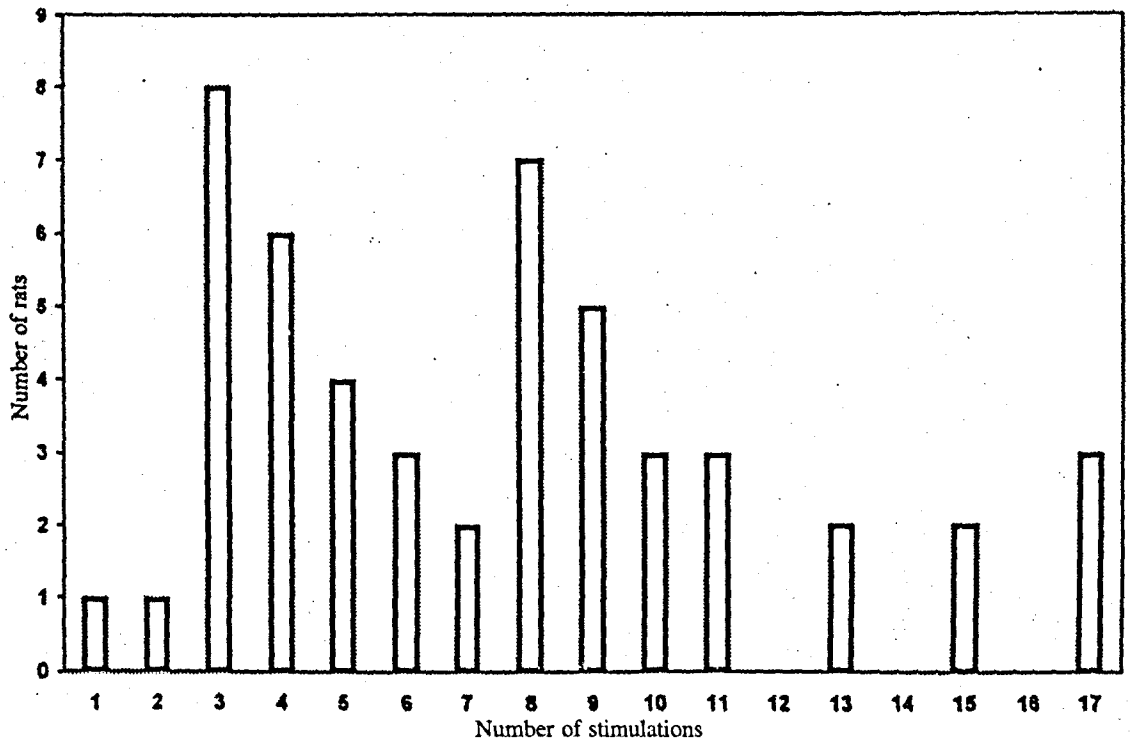

Fig 1: Frequency distribution of kindling rate in the entire experimental population

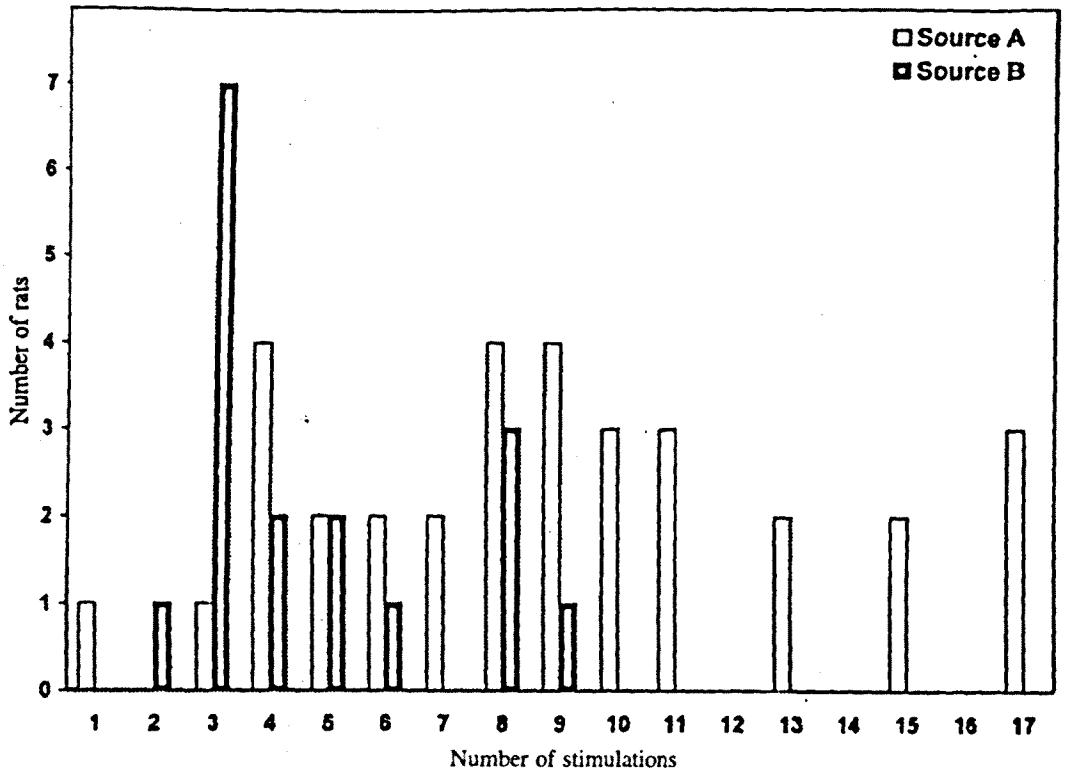

Fig 2: Frequency distribution of kindling rate shown by individuals from Sources A and B.

a possible genetic basis to this phenomenon. Our earlier analysis of six human pedigrees had suggested the possible involvement of an autosomal recessive mutation in HWE (9). It may now be necessary to re-examine these genealogies with a particular focus on the ontogeny of spontaneous seizures in HWE probands in order to detect corresponding phenotypes and examine their underlying genetics.

With the discovery of subpopulations of fast-kindling and slow-kindling rats, we have also begun to explore the possibility of establishing inbred lines of these animals for future classical and molecular genetic studies. Such studies should provide an insight into the genetic basis of HWE, which is essential if we are to understand its mode of inheritance and ætiology, design specific therapies, develop a knowledge base for preventive genetic counseling, and thus, be better able to manage this fairly common epileptic syndrome.

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