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Hyperthermic seizures: an animal model for hot-water epilepsy

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Freely ambulant wistar adult rats of both sexes when exposed to a hot water jet on the head (50°C–55°C) for a period of 8–10 minutes, manifested seizure activity similar to the ones noted in 'hot-water epilepsy' (HWE) in humans. Depth electrode recording from the hippocampus revealed seizure discharges during the ictus lasting from 34 seconds to three minutes, followed by low voltage indeterminate activity and a quiescent resting phase. Seizure initiation was noted to be critically dependent on the rectal temperature of 41.5°C and regional hippocampal temperature of 37°C. There appeared to be no clear evidence for kindling phenomenon. Intervention of hyperthermia by cooling the body after the ictus prevented subsequent occurrence of spontaneous seizures. Pathological study of the brain revealed ischaemic changes in specific topographic areas like Sommer's sector in hippocampus, layer 4 and 5 neurons of the cerebral cortex and reticular neurons in the brain stem—a pathological feature reminiscent of the human epileptic brain. Seizure initiation by hyperthermic stimulation with hot water poured over the head, the progression and the EEG recording the seizure activity in these rats appears to resemble the HWE in human subjects and could thus serve as the first animal model for this form of 'reflex' epilepsy. This has given new insight into the understanding of human HWE. Our preliminary observations in humans has suggested that HWE is a type of hyperthermic seizure similar to febrile convulsion but differs from it with respect to stimulus and rate of rise in temperature in a susceptible individual.

'Hot-water epilepsy' is usually considered as a form of reflex epilepsy, precipitated by a thermal sensory stimulus over the head. This form of epilepsy is commonly seen in South India[1–3] while there have been isolated case reports from other parts of world including Japan, U.S.A. and Canada[4–6]. Usually in India, people bathe every-day and head washing is done generally once every 3–15 days. The practice is to pour large cupfuls of hot water from a bucket in quick succession directly over the head. The seizure is precipitated in certain apparently normal individuals by bathing with hot water on the head, 40–45°C (ambient temperature, 25–28°C). With the initiation of the seizure, the patient drops the mug and the pouring of hot water is discontinued. The body temperature falls to the ambient level soon by cool air around or by moping the body dry by the attendants with a cool towel.

In a large series of 279 cases of HWE evaluated at the Neurology service of National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, South India, the seizure frequency was found to depend on the frequency of head bathing. In 25.4% of these cases, it progressed to non-reflex epilepsy on follow-up[3]. During the initial clinical studies to confirm this phenomenon, with voluntary consent of the patient and close relatives, the seizure could be precipitated in the hospital by pouring hot water over the head of the patient. The hot water stimulus was discontinued immediately after initiation of the attack and the patient was mopped dry.

The clinical characteristics of human HWE is of complex partial seizures or generalized tonic–clonic type. Complex partial seizure semeiology is most frequently reported, occasional ictal EEG recordings in the literature have demonstrated temporal lobe onset[7–9]. However the electrophysiological recordings in humans are generally interictal in nature, because of the obvious difficulty in recording the ictal events. In vitro studies using hippocampal slices have shown that this region of the brain is especially prone to

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epileptogenesis following hyperthermia[10]. In a pathological study of human brains from four confirmed cases of HWE, in two cases (duration of illness 1 year, age 12 years, male and 1.5 years, male) distinct hippocampal involvement with gliosis and ischaemic changes in reticular nuclei of the brain stem were observed. In another two cases, a right thalamic glioma in one and cerebral atrophy with neuronal loss and gliosis in hippocampus on both sides were noted[11]. To understand the pathophysiology and cellular and pharmacological mechanisms modulating this, there is a need for an experimental animal model. This model for HWE must fulfill the criteria of the precipitating stimulus, the ictal events and the EEG that are comparable to those of the human epileptic event[9].

In this study, we describe a rat model, resembling the events of HWE, from initiation of seizures by pouring hot water on the head of rats, to the post-ictal state and the ictal depth EEG recording.

MATERIALS AND METHODS

Eighty Wistar albino rats of both sexes, aged 12–14 weeks (150–230 g) were housed individually, under standard laboratory conditions (25°C, 50% relative humidity, 12/12 hour light/dark cycles). They had ad libitum access to the standard rat pellets (Hindustan Lever Ltd., Bombay) and tap water. The study was carried out according to the ethical guidelines of the Institute for animal experiments, and was initiated only after a week of taming and handling of the rats for acclimatization to the experimental chamber. Initially, 30 rats were randomly distributed into five different groups of six, taking care to match the weights of the animals and were exposed to water jets on the head, the temperatures of the jets being 4°C, 28°C (ambient temperature), 45°C, 50°C and 55°C. During the pilot study, it was found that a hot water jet of 55°C on the head was most consistent in seizure initiation. Hence various aspects of seizure activity initiated by a water jet of 55°C were investigated subsequently in 43 rats in the second phase of the study. Of these, 16 animals were used to study progressive seizure behaviour and 13 to record the rectal temperature profile during the pre-ictal and post-ictal periods. All these were subjected to post-ictal cooling to ambient temperature as in human beings, whilst seven were exposed to hyperthermia but without post-ictal cooling. Seven other animals had bipolar electrodes implanted in the hippocampus to record the EEG. Three animals received hot water to the body only, whilst three animals were not subjected to any stimulation, serving as controls.

Hot water stimulation

The rats were exposed to water jets on the head, using a glass syringe of 10 cm^3 capacity. The jet was directed at the vertex of the rat's head, the rat being placed in a $40 \times 30 \times 15$ cm plastic chamber. The chamber had a fine stainless steel mesh at the base, 6 cm above the bottom, to facilitate continuous drainage of the water, thus avoiding the immersion of the body in the warm water. The rats could move freely in the chamber, above the mesh, during the stimulation. The velocity of the water jet was found to be 13.04 m/second (determined by Bernoulian theorem, mean ± S.D. 0.1 m) and it was delivered at a rate of 30 jets/minute (timed by Metzel metronome). The maximal duration of stimulation was 10 minutes for groups of rats exposed to 4°C and 55°C water jets, and 20 min for the other three groups. These time points were determined by our preliminary studies, when the animals developed either seizures or appeared exhausted, withdrawing to the corner of the chamber and sitting immobile. Seizure initiation was the end point of stimulation in the animals who developed them. Two minutes after the seizure, the rectal temperature of the rats was restored to normal resting level, by pouring tap water (ambient temperature) over the head and body for two minutes. These animals were gently dried with a soft cloth towel, and returned to the home cage. The interstimulation resting period was 24 hours. The stimulation was carried out for a maximum period of 16 days in all the rats, to record any progression in seizure pattern and drop in seizure temperature threshold. In the group of rats exposed to water jets of 4°C however, only five trials were made, and none of them developed seizures. These were gently warmed under a light and returned to the cage. Three animals had hot water (55°C) bathing of the body only, avoiding the head, to raise the rectal temperature to 41–42°C. They were subjected to five stimulation cycles on consecutive days. None of these animals had seizures during the stimulation.

Electrode implantation

As the hippocampus is found to be the site especially prone to epileptogenesis in response to

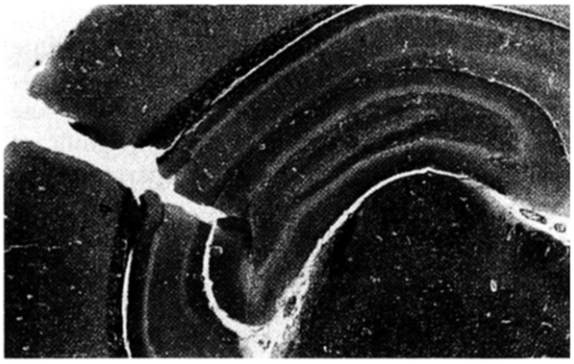

Fig. 1: Photograph showing the electrode track in the hippocampus.

hyperthermia in vitro, and is the site affected by HWE in human brains, this area was chosen for electrode implantation and EEG recording in our animal model. Bipolar electrodes of stainless steel wire of diameter 0.1 mm, with an oblique interelectrode distance of 0.5 mm and insulated with epoxy resin except at the tips, were prepared in the laboratory. They were stereotactically implanted into the right hippocampus of the rats under chloral hydrate anesthesia (400 mg/kg body weight i.p.) using the standard coordinates (2.6 mm behind bregma, 4.6 mm laterally; and 7.5 mm below the cortical surface)[12]. The electrodes were anchored with three eye glass screws using dental cement and liquid acrylic. The same electrodes served for EEG recording as well as for recording the regional hippocampal temperature. On completion of the study, the rats were anaesthetized with chloral hydrate (400 mg/kg i.p.). Hearts were perfused with 0.9% saline followed by 10% buffered formalin. The electrode track was confirmed on paraffin sections stained with cresyl violet (Fig. 1).

RECORDING

Behavioural seizure

The nature of seizure behaviour and its progression with repeated stimulation was observed. Latency and duration of the seizure was recorded visually and using two timing devices.

Temperature threshold

Rectal temperatures were recorded in all the rats with the bulb of the thermometer introduced to a fixed distance. Regional temperatures in the hippocampus were recorded using a thermode developed in our laboratory, the bipolar electrodes serving as probes. The resting temperature and the temperatures at seizure initiation ('threshold') and after post-ictal cooling were recorded. The rectal temperature profile during the period of seizure initiation and progression was recorded in 19 rats, on three occasions. Among these, 13 rats were exposed to 55°C—and six to 50°C—water on the head. The rectal temperature of the animals exposed to water at 55°C was recorded at the initiation of exposure to hot water and at 3, 7 and 10 minutes. In the group of rats exposed to 50°C the rectal temperature was also taken at 15 and 20 minutes as it was found that these animals required longer stimulation to develop seizures.

EEG

In the electrode-implanted rats EEG was recorded at the resting, ictal and recovery phases using a Polyrite physiograph. Random interstimulus recordings were also carried out to look for spontaneous interictal seizure discharges. The freely-moving rats were connected to the EEG recorder only at the time of recording.

Pathology

The deeply anaesthetized animals were intracardially perfused with 20 ml of normal saline followed by 10% buffered formalin 24 hours after the last stimulation. The brains were removed from the skull and kept in the same fixative for 6–7 days, then processed for serial paraffin sectioning (10 μM thick). The brains of three animals which not exposed to any form of hot water stimulation, were processed simultaneously as a control. The sections were stained with H.E., cresyl fast violet for Nissl substance and Luxol fast blue for myelin.

Human HWE

Following this study in rats, in order to evaluate whether similar phenomena occur in human subjects, a pilot study was conducted with 20 healthy human volunteers with no history of seizures and six patients known to suffer HWE. Seizures were induced in the patients under laboratory conditions and video recorded (following informed, written consent of the patients).

Serial oral temperature was recorded at different time intervals: resting, before head bath, mid bath, at the end of the bath, 5 and 10 minutes after the bath.

RESULTS

Of the 43 rats exposed to 55°C water on the head, 32 rats developed seizures on every occasion (mean of 14 trials). The remaining 11 did not develop seizures even after six repeated exposures of more than 10 minutes duration. These were considered to be seizure-resistant animals. The six rats exposed to 50°C water jets had seizures on 11 out of 14 trials. During the remaining three trials the hot water provocation was terminated as there were no seizure. None of the other rats exposed to 4°C (5 attempts) or 25°C and 45°C (14 attempts) had manifested any form of seizures. The animals that appeared exhausted following the stimulus and refractory to seizure induction, remained normal during the follow-up period of 3–6 months.

Normal resting rectal temperature of the adult Wister rats was 37°C while the hippocampal region measured at 35.5°C. In the susceptible animals, the seizures occurred following the very first trial of exposure to hot water, at a mean critical rectal temperature of 41.5°C and corresponding brain temperature of 37°C, (Fig. 2), at a mean latency of 8.0 minutes (55°C group) and 18.6 minutes (50°C group), respectively. The duration of seizures varied from 30 seconds to 3 minutes. This was followed by a 3–4 minute post-ictal quiescent phase. The clinical seizure consisted of clonic movements involving the limbs, trunk and neck. There was no significant variation in the ictal threshold temperature, the latency, duration or pattern of seizures during the 14 repeated trials in this group of animals.

The rectal temperature profile, during the period of hot water stimulation, showed a steeper rising curve in rats exposed to 55°C than in those exposed to 50°C. The seizure-resistant rats showed a gradual rise in temperature curve, in contrast to those that were seizure prone. Temperature profiles recorded in seizure prone animals, on three separate occasions showed no significant variation.

Depth electroencephalography showed seizure discharges in the form of high voltage spikes (100–200 μV; 5–6 Hz), polyspikes and sharp waves lasting 40–45 seconds followed by spike-wave discharge (300 μV, 3–5 Hz) for 15–18 seconds corresponding to the clonic phase of the seizure observed (Fig. 3). This was followed by

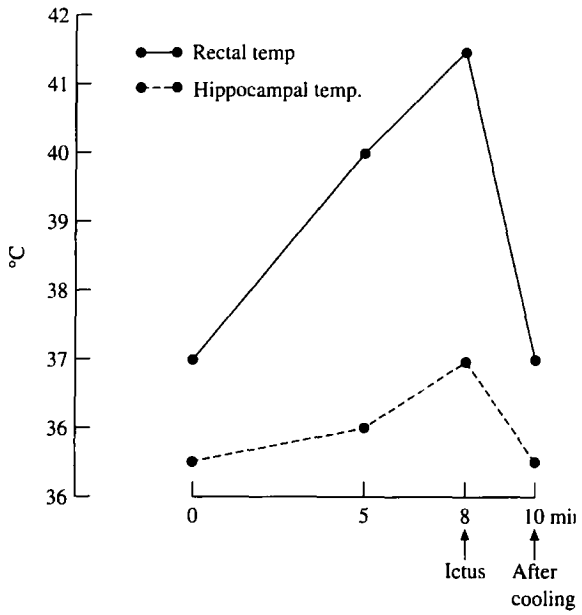

Fig. 2: Graph showing hippocampal and the corresponding rectal temperature profiles following hot water stimulation.

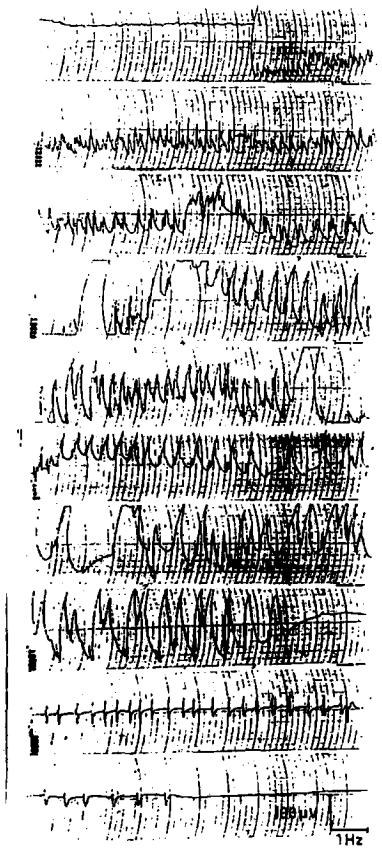

Fig. 3: EEG tracing from the hippocampus through stereotaxic depth electrodes showing pre-ictal, ictal and post-ictal phase in the rat.

low voltage (2–5 μV) indeterminate activity corresponding to the post-ictal quiescent phase lasting about 30 seconds. No spontaneous inter-ictal seizure discharges or behavioural seizures were observed in rats, of any group.

During the initial phase of the study seven rats exposed to hot water jets without post-ictal cooling developed a prolonged post-ictal quiescent phase followed by spontaneous recurrent seizures during the next 24–28 hours, leading to death within seven days. This is similar to status epilepticus found in some of the patients studied. Following this observation, in order to mimic the events in the human reflex epilepsy pattern, immediate cooling of the body of the rats with tap water (25°C) for about 2–3 minutes was introduced to the protocol. With the introduction of this measure, none of the animals developed spontaneous seizures and had only hot water-induced seizures. Among the rats subjected to 55°C water jets and no post-ictal cooling, it took 12 minutes (mean) for the rectal temperature to return to the initial base line level, whilst in those subjected to post-ictal cooling, the basal rectal temperature was reattained in two minutes.

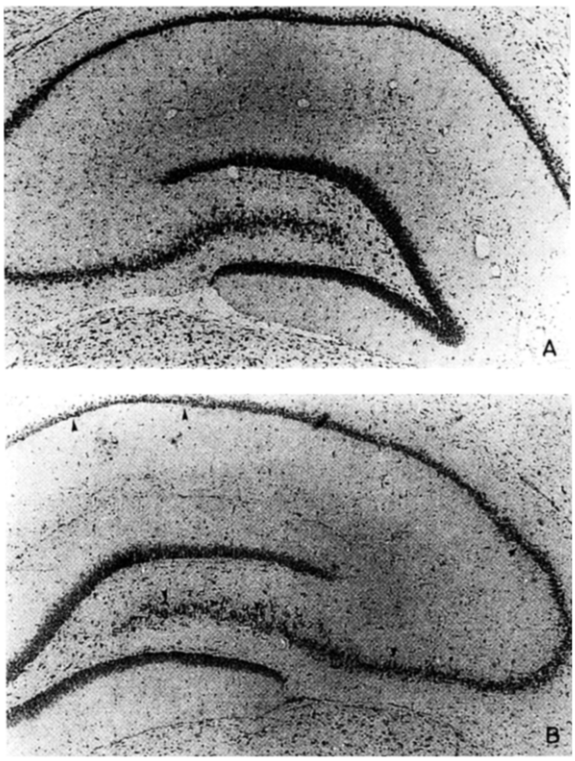

Fig. 4: a, cytoarchitecture of the hippocampus in control rats. Nissl. × 80. b, Ischemic change in neurons of CA 4-5, CA 3, CA 1 areas (arrows) in hippocampus in the animal following seizure. Nissl. × 80.

PATHOLOGY

The two animals which had seizures following hot water jets on the head and were subjected to post-ictal cooling, during the 14 trials (to mimic the events in the clinical setting), revealed varying degrees of anoxic changes in the brain. In the hippocampus, many dark shrunken and twisted neurons were seen in CA1 (Fig. 5c) and CA4-5 (hilar) zones (Figs 4b and 5b). There was no inflammation or appreciable microglial response. Some of the large reticular neurons of the brain stem and the neurons of the thalamus were basophilic, shrunken and had irregularly distorted processes. In the cerebellum, focal Purkinje cell loss and anoxic changes were noted. The affected neurons were interspersed between relatively preserved ones, the latter being predominant.

Brains of the three animals which had recurrent spontaneous seizures for a period of 24–48 hours (55°C jets on the head and no post-ictal cooling), on histological examination, revealed anoxic changes of the neurons in the same topographic areas, e.g. the hippocampus, brain stem and cerebellum, as in the former group, but which were more pronounced. On visual assessment, the cortical neurons of layers 3-4-5 in the frontal and parietal cortex, but not in the cingulate area, had undergone anoxic damage. Even the relatively preserved ones had depleted Nissl substance in the soma. The pathological features in the brains of these seizure-prone animals were asymmetric, one hemisphere being more involved than the other.

Histological features of the brains of three seizure-resistant animals and the three controls (not exposed to heat stimulation) were essentially similar and indistinguishable. Occasional anoxic neurons were randomly observed in the hippocampus and cerebral cortex. However, the brains of the two rats exposed to hot water on the body only, and which did not manifest seizures, had neuronal changes suggestive of anoxia in the CA4-5 (hilar) zone of Sommer sector, but not in the CA_3, CA_2 and CA_1 zones. The cerebral cortical neurons showed variable anoxic changes. There was no appreciable pathology in the white matter of the brains of the animals studied. The glial elements and vessels were unremarkable on routine histological evaluation.

Human HWE

In non-HWE human volunteers, hot water head baths resulted in a 0.5–0.6°F rise in oral

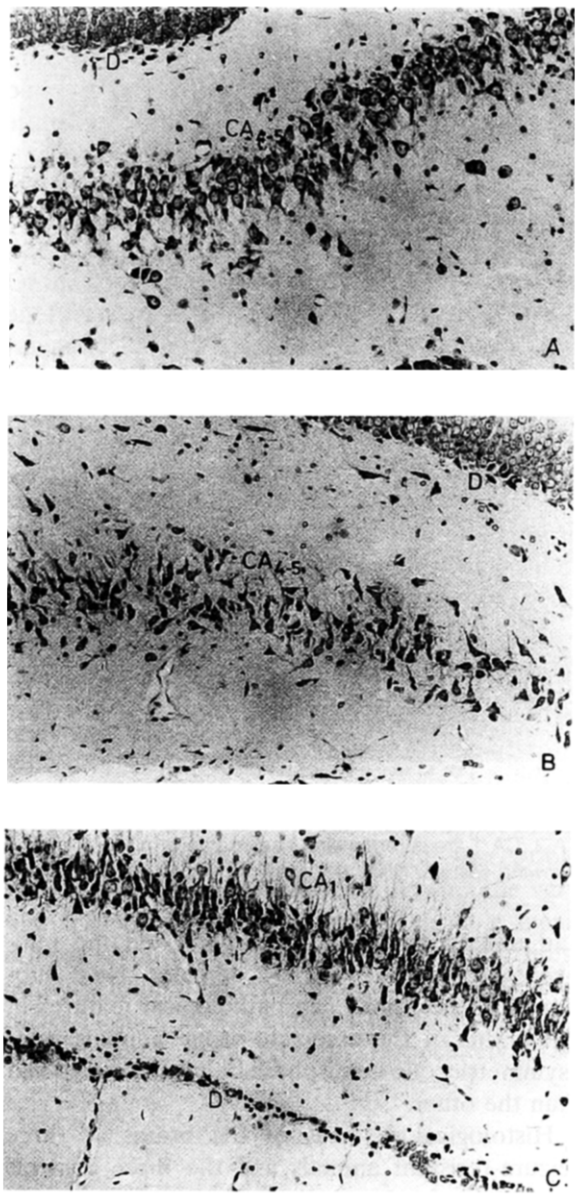

Fig. 5: a, Well preserved neurons in CA 4–5 area of control animal. Nissl. × 320. b, Ischemic change in the neurons of CA 4–5 zone of hippocampus in the epileptic animal (D-Dentate fascia). Nissl. × 320. c, Ischemic change in the pyramidal neurons of CA 1 area in hippocampus. Note depletion of the granular neurons of dentate gyrus (D) also. Nissl. × 320.

temperature, with return to basal level immediately after the bath. In patients with HWE, a rapid rise in oral temperature of 2.0–2.5°F (mean, 2.07°F) was recorded within 2–3 minutes of the hot water head bath. Four of the patients had clinical seizures during this provocation in the laboratory. The fall in oral temperature in these patients was also slow and it failed to return to basal level even 10 minutes after the bath.

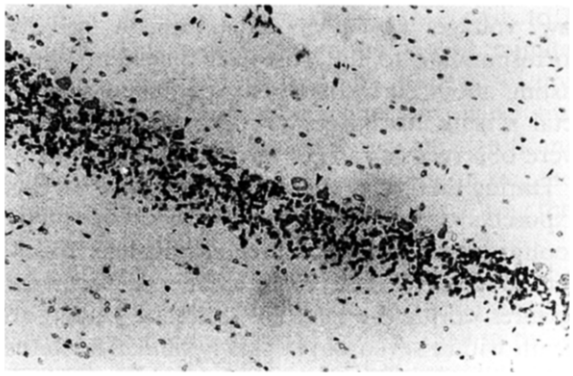

Fig. 6: Ischemic change in the Purkinje cells of cerebellum in the rat following seizure. Nissl. × 320.

DISCUSSION

Reflex or stimulus sensitive epilepsy has been recognized for many years[13,14]. Epilepsy precipitated by the stimulus of hot water bathing has been frequently reported as 'hot water epilepsy'[1–3], or 'water immersion epilepsy'[4,15–16]. The exact mechanism of this type of epilepsy is not clear. Stensman and Ursing[7] have suggested complex tactile and temperature-dependent stimuli as the probable inducing factors in HWE, the seizures manifesting with complex symptomatology. The ictal and interictal scalp EEG recording in these patients indicated temporal lobe origin of the seizure discharges. Szymonowicz and Meloff[8] suggested that there could be structural lesions in the temporal lobe in these cases. It is still unknown whether the mechanism of seizure activity depends on locally increased neuronal excitability or the involvement of deeper structures. Hyperthermia was found to produce seizures in experimental animals (Sprange Dawley Strain) when the rat pups were exposed to infrared lamps[17] or hot air[18], or when adult rats were allowed to swim freely in heated pools[19]. However, none of these models simulated the real situation of a 'hot water bath' producing reflex epilepsy, described from South India. Further, ictal EEG recording was not possible in the human subjects due to the practical limitations associated with simultaneous pouring of water on the head and recording. This problem has been obviated in this rat model by using stereotactically implanted hippocampal electrodes, and carrying out ictal depth EEG recordings[9]. In the present study, the rectal temperatures and the regional temperatures of the hippocampus were recorded at the time of seizure activity, and thus demonstrate the critical

threshold of temperature that induces seizures in this strain of rat.

In this study, when post-ictal cooling of the rats was carried out, there was no evidence of progressive spontaneous seizure patterns or alteration in critical temperature for seizure induction during the subsequent stimulations. The development of spontaneous seizures leading to death in the rats not subjected to post-ictal cooling, does not appear to represent kindling phenomenon. Hyperthermic seizures in experimental animals are used as models to study human febrile convulsions. Protection of the rats from progressing to spontaneous seizure activity by post-ictal cooling emphasizes the role of therapeutic intervention to reduce body temperature, thus altering the pathomechanism of seizure activity, in this form of reflex epilepsy.

The topographic distribution of the post-ictal ischaemic changes of the neurons in the hippocampus, the cerebral cortex and reticular formation are reminiscent of the features observed in human epilepsy. In these rats no gliosis was observed following the seizures as demonstrated in the earlier studies[20]. However it may be necessary to follow these animals for longer periods to evaluate the glial response. The neuronal changes observed appeared to be in response to the seizure activity, as similar changes are not noticed in control rats of the same strain and age. The greater degree of anoxic changes observed in the animals who continued to have spontaneous seizures following induction may represent changes usually observed in those who succumb to status epilepticus. The presence of fine nuclear debri in the neuropil of the hilar zone of the Sommer sector in the brains of the animals exposed to hot water on the body and had no seizures is rather curious and its significance is not clear. The pathomorphological features suggest a process of apoptosis. This needs further study and validation.

The rapid rise in rectal temperature following thermal stimulus in seizure-susceptible rats in contrast to the seizure-resistant ones, and differential gradient of the temperature curve in response to 55°C and 50°C of hot water jets on the head, indicate the possible role of the thermoregulatory centre in initiating the seizure discharge. Furthermore, the study suggests certain constitutional–genetic traits among the wistar strain that make some rodents 'seizure-resistant' and others 'seizure-prone', as observed in the human population[5]. In clinical practice, nearly 16–38% of patients with hot water epilepsy develop non-reflex spontaneous epilepsy within 1–3 years after the onset of HWE[2,21]. Whether this could represent an element of hyperthermic kindling phenomenon in the evolution of this disease process, as hypothesized by Satischandra *et al*[3] in their earlier publication, needs to be evaluated.

Our preliminary observations in human HWE subjects suggest that in the susceptible human population, this special form of induced hyperthermia could be responsible for causing HWE, a distinct variant of hyperthermic seizures[22]. In our earlier report, only 20 (14%) of 279 patients had previous history of febrile convulsions[3]. We postulate that the HWE patients probably have an aberrant thermoregulatory system and are sensitive to 'rapid rise' in temperature. They manifest seizures with 'rapid spurt' in regional temperature, following hot-water stimulation over the scalp[22]. The rodent model described simulates the human situation and further gives new evidence that human HWE is not a 'true' reflex epilepsy but a hyperthermic seizure. Studies are in progress to elucidate the modulating factors involved in initiation and propagation of the seizure activity and the pharmacological strategies to abrogate this special form of reflex epilepsy.

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