Epilepsy Research (2013) **106**, 29—34

journal homepage: www.elsevier.com/locate/epilepsyres

Hyponatremia augments kainic-acid induced status epilepticus in the mouse: A model for dysmetabolic status epilepticus

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Received 3 March 2013 ; received in revised form 14 May 2013; accepted 25 May 2013
Available online 21 June 2013

KEYWORDS
Status epilepticus;
Kainic acid;
Hyponatremia

Summary Status epilepticus (SE) is a dreaded neurological emergency. A reignited interest in SE has resulted in a more adaptive use of treatment protocols. More knowledge on SE of various aetiologies is therefore needed. We are interested in treatment of SE under hyponatremia, and have here evaluated whether SE induced by systemic kainic acid could be a suitable platform for such studies. Acute hyponatremia was induced in C57/BL6 mice by intraperitoneal injection of dDAVP and water loading. Hyponatremic mice displayed an increased frequency of epileptiform spikes on EEG and 5/9 hyponatremic mice displayed electrographic seizures. After kainic acid (20 mg/kg) treatment, hyponatremic mice displayed significantly longer time with electrographic seizure activity, which was also seen after treatment with diazepam (20 mg/kg). We conclude that hyponatremia augments kainic acid-induced SE, This model might be a valuable platform for studies on treatment of SE in hyponatremia.

Introduction

Status epilepticus (SE) is a dreaded neurological emergency associated with high mortality. As our understanding of SE increases, it is clear that different aetiologies of SE respond differently to treatments. Suitable experimental assays to evaluate different treatments of SE under various conditions are therefore needed.

Hyponatremia is a well-known aggravating factor for seizures (Bleck, 2009; Halawa et al., 2011; Martindale et al., 2011). The condition can arise for several reasons, for instance the use of diuretics in the elderly population, side effects of antiepileptic drug treatment, or from psychogenic polydipsia. The speed with which the hyponatremia develops affects the seizure risk, and several cases of seizures due to acute hyponatremia as a consequence of water intoxication exist in the literature (O'Connor, 1985; Primavera et al., 1995). Hyponatremia is significantly associated with SE refractory to treatment, indicating the importance of studies on this particular dysmetabolic condition (Holtkamp et al., 2005).

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0920-1211/$ — see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.eplepsyres.2013.05.010

There is little experimental data on SE in hyponatremia. Seizures in hyponatremia have been studied mostly in the context of seizure thresholds or very severe hyponatremia causing brain oedema, herniation and death. Hypotonic hyponatremia is known to reduce the threshold for electrically induced seizures (Sofia and Barry, 1977; Swinyard et al., 1955), as well as chemically-induced seizures in relation to renal failure (Nagata et al., 2003). These studies however, did not clarify the effect of hyponatremia on SE severity or duration.

There are several models of SE in rodents. Among the simpler ones are chemoconvulsant-induced seizures, which have the advantages of not requiring a kindling setup. Several chemoconvulsants, such as pentylenetetrazole, pilocarpine, or kainic acid can be used to induce SE. Based on the literature and our previous experience (Borges et al., 2003; Huang et al., 2009; Zelano et al., 2012), KA seems comparably easy to control, robust in the induction of SE, and has an increased survival — which would potentially lessen variability. We therefore asked if KA-induced status epilepticus could be a suitable model for experiments on SE under acute hyponatremia.

We subjected mice to a moderate degree of acute hyponatremia induced by water loading—and evaluated the effect on KA-induced SE. We report that hyponatremia in itself induced epileptiform activity on EEG and that KA-induced SE was augmented in hyponatremic mice. We conclude that KA-induced SE is a suitable model for future studies on SE under dysmetabolic conditions.

Materials and methods

Mice

Female mice C57/BL6 mice, more than seven-week old, from Taconic® were used. All mice were group housed, maintained on a 12-h day/light circle and cared for according to present animal regulations. The experiments were approved by the Uppsala animal ethics committee, approval number C345/11.

EEG

Electroencephalography (EEG) traces were recorded using the cable-tethered PAL-8200 system (Pinnaclet technology Inc, Lawrence, KA, USA). After anaesthesia and placement of epidural electrodes, the mice were treated with buprenorphin for pain relief and allowed to recover for at least three days prior to EEG-recordings. The preamplifier setting was 100x and the signal filtered at 40 Hz. The electrodes were placed according to the manufacturers instructions in six holes drilled through the skull to the dura (1,5 mm lateral to the midline, 2 mm anterior, 2 mm posterior, and 5 mm posterior to the Bregma, respectively). Three channels were recorded ipsilateral left frontal, cross-cortical frontoparietal, and cross-cortical occipital. Hyponatremia was induced by intraperitoneal injection of 1-deamino-8-D-arginine vasopressin (DDAVP) 0,5 μg/kg diluted in sterile water equivalent to 7.5% of body weight, a modification of the protocol described by

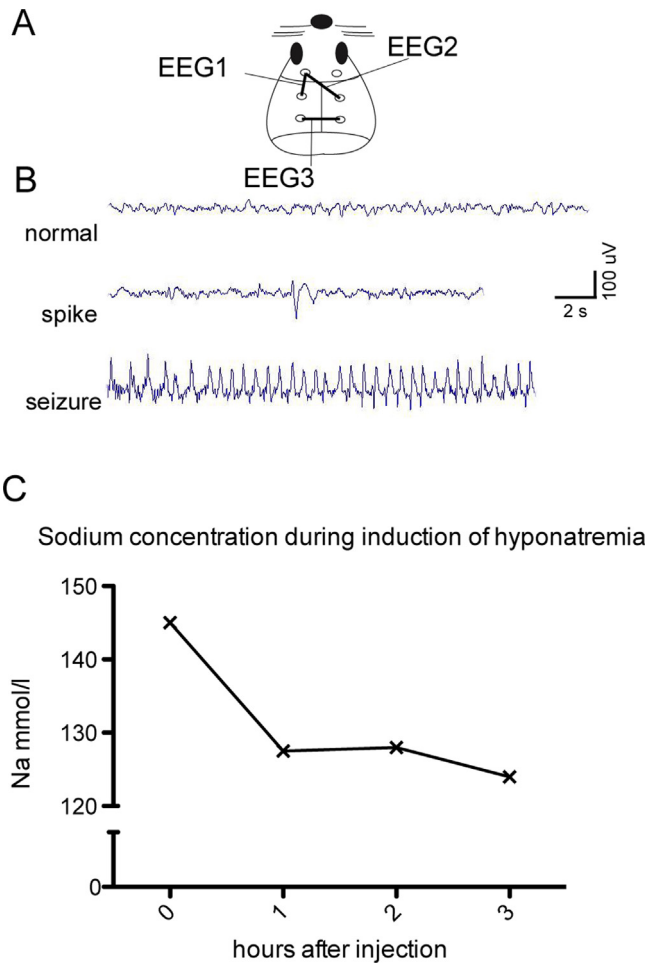

Figure 1 EEG-setup and induction of hyponatremia. (A) Three EEG-channels were monitored, based on six epidural electrodes placed as indicated. (B) Representative recordings of EEG-traces showing normal background, spike (defined as short high-amplitude — more than 2× background — events), and seizure (defined as high-amplitude repetitive events of epileptiform morphology). (C) Hyponatremia was induced by a single injection of water and dDAVP. Sodium concentration at different time points after the injection is indicated, data points indicate single measurements from one animal per time point.

Vajda (Vajda et al., 2002). For kainic-acid treatment, mice were intraperitoneally injected with 20 mg/kg kainic acid. (P6503, Sigma—Aldrich, Stockholm, Sweden).

Blood analysis

Blood analyses were performed immediately *post-mortem* using an i-Stat® analyzer (Abbot, Sweden). Animals were deeply sedated with an overdose of isoflurane and decapitated. Arterial blood from the neck was immediately collected in test cartridges (GC8+). Electrolytes from six mice from each treatment group were analyzed after the experiment.