Down-regulated expression of aquaporin-4 in the cerebellum after status epilepticus

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Received: 27 March 2016 / Revised: 15 October 2016 / Accepted: 9 November 2016 / Published online: 14 November 2016
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Abstract Status epilepticus (SE) is a common neurological condition associated with high rates of mortality and permanent brain injury. SE usually leads to neuronal death which may be accompanied by edema, epileptogenesis and learning impairment. Aquaporin-4 (AQP4), is a transmembrane water channel protein in the neuropil of the central nervous system that has an important role in water transport in the brain; AQP4 expression is altered in many pathological conditions such as changes in the blood–brain barrier and/or astrocytic activation, including seizures. AQP4 was shown to be downregulated in the piriform cortex and the hippocampus after SE. Although it is normally expressed at a high level in the cerebellum, little is known about AQP4 levels in the cerebellum following SE. We addressed this in the present study in a mouse model of pilocarpine-induced SE. We found that AQP4 expression was reduced from 3 h to 3 days after SE, with the levels recovering on day 7. Moreover, mice in the acute post-SE stages exhibited impaired motor coordination and learning. These results indicate that cerebellar damage following SE involves changes in AQP4 expression.

Keywords Status epilepticus · Cerebellum · Aquaporin-4 · Edema · Motor coordination · Motor learning

Introduction

Status epilepticus (SE) is a common neurological condition associated with high mortality (DeLorenzo et al. 1995) or permanent brain injury (Itoh et al. 2015). It is defined as continuous seizure activity lasting longer than 5 min (Rice and DeLorenzo 1998), and usually leads to neuronal death (Fujikawa 1995; Freichel et al. 2006; Itoh et al. 2015) accompanied by epileptogenesis and learning impairment (Rice and DeLorenzo 1998; Stewart and Persinger 2001) as well as edema (Emerson et al. 1999; Kim et al. 2009, 2010; Itoh et al. 2015). The piriform cortex and hippocampus are the brain regions most susceptible to SE-induced damage (Sperk 1994; Covolan and Mello 2000; Kim et al. 2010), while less is known about the effects of SE on the cerebellum.

Aquaporin-4 (AQP4), is a transmembrane water channel protein (Badaut et al. 2002) that is primarily expressed by astrocytes in the central nervous system, especially at the end feet surrounding capillaries and the blood–brain barrier (Nagelhus et al. 2004; Oshio et al. 2004; Costa et al. 2007). AQP4 expression is dysregulated in various neurological disorders characterized by blood–brain barrier changes and/or astrocyte activation including seizures, and plays an important role in the development of edema (Nielsen et al. 1997; Manley et al. 2004). Previous studies have shown that AQP4 expression is down regulated in the piriform cortex and hippocampus following SE (Kim et al. 2010; Lee et al. 2012). AQP4 is highly expressed in the cerebellum (Nico et al. 2002; Hubbard et al. 2015), but it is not known how this may be affected by SE. We addressed this in the present study using a mouse model of pilocarpine-induced SE.

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Materials and methods

Animals

Adult male C57BL/6 mice (3 months, 21.8–24.6 g) were used in this study. Animals had free access to food and water and were maintained under a 12:12-h light/dark cycle. The study protocol was approved by the Animal Care Committees, Nanchong Central Hospital, Second Affiliated Hospital of North Sichuan Medical College.

Induction of SE

SE was induced in mice by intraperitoneal administration of a low dose of pilocarpine hydrochloride (100 mg/kg) (Sigma Aldrich) every 20 min until the onset of SE (Groticke et al. 2007; Muller et al. 2009). To alleviate peripheral cholinergic side effects, methylscopolamine nitrate (1 mg/kg; i.p., Sigma Aldrich) was injected 30 min before the application of pilocarpine. A similar volume of 0.9% (w/v) sterile saline was injected into control animals. SE was defined as continuous stage 4 or 5 seizure activity according to the Racine scale (Racine 1972). Three injections are usually needed to induce the first seizure; if SE was not induced after five injections, no further attempts were made for that mouse. All mice that developed SE lasting for several hours received diazepam (10 mg/kg) after 90 min to terminate seizure activity. The same dose of diazepam was also injected into mice that did not develop SE as well as control mice. 83 mice were distributed into three groups ($n = 28$ in control group; $n = 28$ in SE group; $n = 27$ in no-SE group). Mice ($n = 25$) that died after pilocarpine injections were excluded analysis.

Western blotting

Mice were divided into control ($n = 5$), no-SE ($n = 5$), and SE ($n = 5$) groups and were examined at predetermined time points (3 h, 12 h, 24 h, 72 h and 7 days after SE). Mice (did not come from behavioral tests except at 7 days time points) were sacrificed and the cerebellum was quickly removed, total protein was extracted with lysis buffer (iNtRON Biotechnology, Korea) containing protease inhibitor (Thermo Fisher Scientific Inc., MA, USA). After incubation for 30 min on ice, the homogenate was centrifuged and protein concentration in the supernatant was determined with Micro Protein Assay (Thermo Fisher Scientific Inc., MA, USA). Samples containing 40 μ g total protein were boiled in loading buffer and separated by 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis, followed by electrotransfer to a polyvinylidene difluoride membrane (Millipore, MA, USA), which was blocked in Tris-buffered saline containing 0.05% Tween-20 (TBST) and 5% bovine serum albumin (BSA; Sigma, St. Louis, MO, USA) for 1 h. The blot

was incubated with primary antibodies against AQP4 (Abcam, Cambridge, MA, USA; ab81355, 1:1000) and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (ZSGB-BIO, Beijing, China; TA-08, 1:1000) in TBST at 4 °C for 16 h, washed with TBST then incubated with secondary antibodies for 1 h at room temperature. Target protein band intensity was determined relative to that of GAPDH with Image J software (National Institutes of Health, Bethesda, MD, USA).

Behavioral testing

Motor function, including balance and coordination, was evaluated with the accelerating-rotarod test as previously described (Wei et al. 2011) with some modifications. Mice ($n = 8$ each in control and SE groups, $n = 7$ in no-SE group) were placed on the rotarod facing opposite to the direction of rotation. The initial speed of the rotarod was 4 rpm. After 10 s, the rod was accelerated from 4 to 40 rpm over 4 min and maintained a constant speed was maintained for 1 min. The latency time until the mouse fell off the rod was recorded over a maximum observation period of 5 min. Three trials were performed for each mouse and the data were averaged.

Statistical analysis

Data are presented as mean $\pm$ SEM. One-way analysis of variance (ANOVA) was used to assess differences between two groups and the least significant difference test was used to compare multiple groups. Data from the behavioral test was evaluated by two-way ANOVA. $p < 0.05$ was considered statistically significant. Asterisks represent a statistically significant result compared to saline control group.

Results

Behavioral characteristics and mortality

Pilocarpine-induced behavioral characteristics included hypoactivity, curling up, tremors, head bobbing, and myoclonic movement of the limbs. Rearing with or without falling and jumping occurred at the onset of SE. The mortality rate in the experimental group was 21.36% (25/117), and 68.47% (63/92) of mice developed SE.

AQP4 expression is downregulated in the cerebellum after SE

AQP4 was highly expressed in the cerebellum of control animals. AQP4 levels began to decline ($F = 6.714$, $p < 0.001$) relative to the control group 3 h after SE

($p < 0.05$); at 12 and 24 h, AQP4 expression had decreased to 71.2% ($p < 0.05$) and 58.1% ($p < 0.01$), respectively. AQP4 level was still lower (68.5%) than baseline 3 days after SE, but was slightly higher than at 24 h ($p < 0.05$). AQP4 expression recovered to the baseline level after 7 days (Fig. 1a, b). A obvious changed tendency of AQP4 expression level were observed in each mice, so we can think of expression level of AQP4 is not affected by sample number.

We also examined the expression of AQP4 in the cerebellum of mice in which SE was not induced. The levels were similar to those in the control group and did not change over time following SE ($F = 0.974$, $p = 0.454$) (Fig. 1a, c), suggesting that changes in AQP4 expression result from SE and are related to SE intensity.

Mice exhibited impaired motor coordination after SE

Given the important role of the cerebellum in motor balance and coordination, we evaluated motor function in mice after SE with the accelerating-rotarod test. At 1 day after SE, mice showed no changes in test performance as compared to control mice; however, a decreased latency to fall was detected at 2 days ($p < 0.05$), and became more pronounced 3–7 days after SE ($p < 0.01$) (Fig. 2). Furthermore, although performance improved in control mice between days 1 and 7, the same was not true in SE (Fig. 2). Mice that did not develop SE showed better performance than those in the SE group. These results indicate that SE impairs motor balance and coordination over the long term.

Discussion

Epilepsy is a common and severe neurological disorder that can undermine the psychological health and quality of life of patients (Ngugi et al. 2010; Rowley and Patel 2013; Du et al. 2016). Temporal lobe epilepsy (TLE) is the most common form and is usually preceded by prolonged seizures or SE. TLE patients typically exhibit chronic epilepsy with spontaneous recurrent seizures and psychological comorbidities such as anxiety, depression, psychosis, and altered cognition function (Elger et al. 2004; Murphy 2013). Pilocarpine-induced SE has been a useful model for studying epilepsy because it has similar characteristics to human TLE (Cavalheiro et al. 1996; Curia et al. 2008; Xing et al. 2016). The hippocampus, piriform cortex, thalamus, amygdala, and neocortex are brain areas that are frequently damaged after SE (Turski et al. 1983; Cavalheiro et al. 1996), which is usually accompanied by edema (Manley et al. 2000; Haj-Yasein et al. 2011). We report here for the first time that the cerebellum is also altered by pilocarpine-induced SE.

High mortality rates have been reported in mouse models of SE induced by administration of a single high dose of pilocarpine (Buckmaster and Haney 2012; Oliveira et al. 2015). In this study, we successfully induced SE with repeated injections of a relatively low dose of the drug; this reduced the mortality rate, making it a more suitable SE model.

AQP4 is a bidirectional water channel membrane protein that is primarily localized in end feet and membranes

Fig. 1 Relative expression level of AQP4 in the cerebellum after SE. **a** AQP4 expression was gradually downregulated after SE and reached at the lowest level 24 h after SE; however, the level returned to baseline 7 days after SE. AQP4 expression in the cerebellum of mice that did not develop SE was unaltered. **b, c** Quantitative analysis of AQP4 expression in the cerebellum of mice that did (**b**) and did not (**c**) develop SE at different time points. ($n = 5$ in each groups). * $p < 0.05$; ** $p < 0.01$ versus saline control group. CON, Control mice

Fig. 2 Effect of pilocarpine-induced SE on mice motor function. Mice showed poor performance in the accelerating-rotarod test following SE. The latency to fall off the rod was shorter than in control mice from 2 to 7 days after SE. Learning ability increased in control mice from 1 to 7 days after SE; this was not observed in SE mice, while the no-SE group showed no obvious impairment in motor function. (n = 8 each in control and SE groups, n = 7 in no-SE group). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ versus saline control group. CON, Control mice

of astrocytes in the central nervous system (Hubbard et al. 2015; Zhang et al. 2015), and maintains water homeostasis by regulating the transport of water molecules (Papadopoulos and Verkman 2013). AQP4 is involved in the occurrence of edema in pathological conditions such as stroke, brain injury, and epilepsy (Manley et al. 2000; Kim et al. 2010; Lee et al. 2012; Vella et al. 2015; Zhang et al. 2015). Although AQP4 is highly expressed in the cerebellum, little is known about how this is affected by SE. We report here that AQP4 protein level gradually decreased after SE but recovered to the baseline by day 7, indicating that like other brain regions, the cerebellum is affected by SE, although recovery took place more rapidly. This downregulation in AQP4 also suggests that vasogenic edema occurred in the cerebellum in the acute stage after SE, since AQP4 known to be downregulated during this process (Fukuda et al. 2013; Zhang et al. 2015); moreover, it may be related to SE intensity since we did not observe any changes in AQP4 levels in the cerebellum of mice that did not develop SE.

Mice with pilocarpine-induced SE exhibit behavioral alteration, including anxiety and depression-like behaviors and cognitive disturbance (Groticke et al. 2007; Oliveira et al. 2015). The cerebellum is critical for motor balance and coordination (Mauk et al. 2000; Glickstein et al. 2009). In this study, mice in the acute stages following SE showed poor performance in the accelerating-rotarod test, although this differs from the findings of a previous study (Oliveira et al. 2015). In contrast, in the constant-speed rotarod test, mice did not show impairment motor coordination. It is possible that the mice had recovered sufficient cerebellar function by the chronic stage to perform normally on this test, which is less difficult than the accelerating-rotarod

test. Motor learning ability is also evaluated by the accelerating-rotarod test (Sharma et al. 2005), since mice are required to adjust step frequency to adapt to the changing speed. In our study, mice that developed SE showed poor learning ability relative to controls and mice that did not develop SE. It is worth noting that 7 days after SE, the amount of time that mice stayed on the rod was less than control mice, although AQP4 expression level had recovered by this time point. This is expected, since motor learning ability consists of a fast learning phase followed by a slow consolidation phase (Shadmehr and Brashers-Krug 1997; Shadmehr and Holcomb 1997; Medina and Mauk 2000; Clopath 2012).

This is the first study to report that the cerebellum is affected by SE. AQP4 expression was down-regulated in the acute stage following SE, but recovered to a normal level after 7 days, indicating that edema was transient. This change in AQP4 expression was accompanied by an impairment in motor coordination and learning ability. However, the precise relationship between downregulation of AQP4 in the cerebellum and impaired motor learning remains to be elucidated, for instance by using a knockout mouse model. In addition, the cerebellar expression of AQP4 during the chronic stage after SE must be examined in order to determine whether there is permanent damage caused by SE.

Acknowledgements The works were supported by Grants from the Department of Neurosurgery, Nanchong Central Hospital, Second Affiliated Hospital of North Sichuan Medical College.

Compliance with ethical standards

Conflict of interest The authors declare that have no conflict of interest.

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