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Research Report

Abnormal expression of epilepsy-related gene *ERG1/NSF* in the spontaneous recurrent seizure rats with spatial learning memory deficits induced by kainic acid

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Abstract

Previous epilepsy-related gene screen identified a spontaneous recurrent seizure (SRS)-related gene named epilepsy-related gene (*ERG1*) that encodes *N*-ethylmaleimide-sensitive fusion protein (NSF). To explore whether spatial learning memory deficits are relevant to SRS and whether hippocampal NSF expression is altered by SRS, we used the kainic acid (KA)-induced epilepsy animal model. SRS was monitored for 3 weeks after injection of a single convulsive dose of KA. KA-treated rats with SRS, KA-treated rats without SRS, and saline-treated rats were then measured in Morris water maze. In this spatial learning task, KA-treated rats with SRS performed poorer compared to those without SRS and those treated with saline. During the subsequent probe trials, KA-treated rats with SRS spent less swim path and time in the target quadrant but more swim path and time in the opposite quadrant, and showed fewer platform crossings. Moreover, in situ hybridization and immunohistochemistry showed that both *ERG1*/NSF mRNA and NSF immunoreactive expression were down-regulated in the CA1 and dorsal dentate gyrus cells (dDGCs) of the hippocampus, and interestingly, tyrosine hydroxylase (TH) immunoreactive dopamine (DA) neurons were lost in ventral tegmental area (VTA) in the KA rats with SRS. These data demonstrate that SRS impairs spatial learning memory and suggest that the down-regulation of NSF expression pattern in the hippocampus and the loss of DA neurons in VTA might contribute to the spatial learning memory deficits induced by SRS.

Theme: Disorder of the nervous system
Topic: Epilepsy: basic mechanisms

Keywords: Epilepsy-related gene; Spontaneous recurrent seizure; *N*-ethylmaleimide-sensitive fusion protein; Kainic acid; Spatial learning memory; Ventral tegmental area

Abbreviations: ERG1, epilepsy-related gene; SRS, spontaneous recurrent seizure; NSF, *N*-ethylmaleimide-sensitive fusion protein; KA, kainic acid; DGCs, dentate gyrus cells; TH, tyrosine hydroxylase; DA, dopamine; VTA, ventral tegmental area; TLE, temporal lobe epilepsy; SD, Sprague–Dawley; PBS, phosphate buffer saline; BSA, bovine serum albumin; DAB, diaminobenzidine; TR, training quadrant; OP, opposite quadrant; nNOS, neural nitric oxide synthase; LTP, long-term potentiation; LTD, long-term depression; SOD1, superoxide dismutase 1; AMPA, α amino-3-hydroxy-5-methyl-4-isoxazole propionate; SNARE, associated soluble NSF attachment protein receptor

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1. Introduction

Epilepsy, one of the most common neurological disorders, shows major clinic syndromes such as spontaneous recurrent seizures (SRS). In adults with temporal lobe epilepsy (TLE), complex partial seizures have the poorest prognosis of all types of seizures, with about 60–70% of all patients having intractable seizures [18]. Moreover, memory problems are common in human TLE while its mechanism is unclear [1,4,5]. Kainic acid (KA) is a structural analog of excitatory amino acid neurotransmitter-glutamate. A single systemic injection of a convulsive dose of KA results in limbic status epilepticus [3,22], which is followed by long-term SRS [32,34], as well as spatial learning impairments [19,32]. KA-induced epilepsy model has been used widely to study human TLE [12,21]. Recently, KA has also been found to induce progressive death of nigral neurons by unilateral injection of KA in the striatum [8]. Whether a systemic injection of KA could affect dopamine (DA) neurons is not known. Previously, our lab identified an SRS-related gene named epilepsy-related gene (*ERG1*) (GenBank accession no. AF142097), which encodes a *Rattus* homologue of *N*-ethylmaleimide-sensitive fusion protein (NSF) [11]. NSF, an ATPase, plays a key role in docking and/or fusion of transport vesicles in the multi-step pathways of vesicular transport [14,17,35]. These results shed light on the mechanism for chronic epilepsy. But little is known on a possible role of *ERG1/NSF* in chronic epilepsy accompanied with learning disability [11,40]. In the present study, we focused on the effects of SRS on Morris water maze task and the expression patterns of *ERG1/NSF* related to the learning impairment with SRS. Meanwhile, we used tyrosine hydroxylase (TH) immunohistochemistry to examine the DA neurons.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley (SD) healthy rats (Dalian Medical University Animal Center, China) weighing 180–220 g/body were kept on a 12-h light/dark schedule with free access to standard laboratory food and water. The temperature of the room was maintained at 22 ± 1 °C. The research complied with national legislation on the Care and Use of animals.

2.2. Making status epileptic rats

Animals were divided into the experiment group (KA group, $n = 35$) and the control (saline-treated group, $n = 16$) randomly. The experimental rats were injected with KA (Sigma Company, USA, 10 mg/kg, 5 mg/ml) subcutaneously (s.c.). KA was freshly dissolved in 0.9% physiological saline. Saline-treated rats were given the same volume of physiological saline. Rats were behaviorally rated according to the scale of Racine [28]. Seizure stages as defined by Racine are: stage 1, chewing; stage 2, head nodding; stage 3, unilateral forelimb clonus; stage 4, rearing with bilateral forelimb clonus; stage 5, rearing with bilateral forelimb clonus and falling back. Then, during the following days, KA-treated rats' behavior was monitored for 10 h each day for 3 weeks. The criterion of SRS was in the stages from 3 to 5 according to the scale of Racine. The experimental rats with showing SRS were regarded as the KA-treated group with SRS ($n = 19$), those without SRS were KA-treated group without SRS ($n = 16$).

2.3. Morris water maze

Morris water maze (Institute of Material Medicine, Chinese Academy of Medical Sciences) is composed of the monitor with the video camera set in the ceiling, a computerized tracking system (DMS-2), and a circular metal tank (1.20 m in diameter, 0.50 m in height) filled with water (25 ± 1 °C). Four start positions with red mark were located equidistantly around the edge of the maze, dividing it into four equal quadrants. During training and testing, a platform (0.12 m in diameter, 0.24 m in height) was submerged 0.5 cm below the surface of the water. Put the skimmed milk in the water in order to exclude the other factors to effect on spatial learning memory. Distal visual cues outside of the pool and the location of the platform remained constant throughout all experiments.

All rats were trained [7,41] for 3 consecutive days in the Morris water task after the final treatment with KA. Place the rat in the platform for 20 s and then put it into the water facing the wall of the maze in four quadrants consecutively at the same time each day. We kept the rat in the platform for 20 s if the rat reached the platform in 60 s. We guided and placed the rat in the platform for 20 s as repetition training if the rat failed to find the platform within 60 s. The following formal tests began after the training for 3 days. Place Navigation Test: Put each rat into the water from the middle point of quadrant facing the wall randomly every day. The latency and swim path of the rat were monitored by a video and DMS-2, which measured the spatial learning ability in the rat for 4 consecutive days. Spatial Probe Test: Remove the hidden platform at the 5th day of formal tests and then place the rat into the water from the middle point of the edge in the target quadrant. We recorded the latency, the swim path, and the time spent in the training and opposite quadrants in 60 s, which showed the spatial memory ability.

2.4. In situ hybridization

In situ hybridization was done using nonradioactive method with the DIG system according to the manufacturer's instructions. Antisense and sense cRNA probes of *ERG1* labeled digoxingenin-11-UPT generated from the vector using SP6/T7 transcription (Roche). The procedure

and the brain section were processed as described by Guan et al. [11]. The optical density of NSF mRNA expression was analyzed.

2.5. Immunohistochemistry

Animals were deeply anesthetized with 4% Chlorali Hydras (400 mg/kg, i.p.) and perfused transcardially with 1% and 4% paraformaldehyde, respectively. The brain was post-fixed by using 4% paraformaldehyde and was put in phosphate buffer saline (PBS) containing 30% sucrose. When the brain was submerged, 50-μm-thick brain sections were sliced on a vibratome. The above sections were rinsed first in PBS 10 min × 3, then were incubated with bovine serum albumin (BSA) (Bochringer Company, USA) for 30 min. The sections were incubated in the primary antibody (TH-Ab, 1:1000, NSF-Ab,1:100 Sigma and Santa Cruz Biotechnology) overnight at 4 °C. The sections were rinsed in PBS 10 min × 3 and further incubated in the biotinylated-second antibody (Boster Company, P.R. China) at room temperature for 1 h. Then, the sections were rinsed in PBS 10 min × 3 and followed by incubating with avidin–biotin complex A:B:PBS (1:1:400) (Avidin Biotin Complex Kit, Sigma Company, USA) at room temperature for 2 h. Diaminobenzidine (DAB; Sigma Company, USA) was used to detect signals. The control sections were incubated with PBS instead of primary antibody.

HPIAS series colorful pathology photograph system was used to analyze TH immunoreactive DA neurons and NSF immunoreactive granules. The brain sections were observed in 10× microscope. The measure square in the screen is 3120.4 μm^2 (43.1 μm × 72.4 μm, 3.3 × 20). The number of TH immunoreactive DA neurons and NSF immunoreactive granules was measured per measure square.

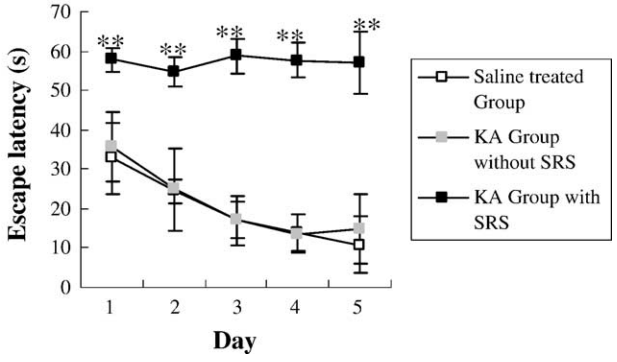

Fig. 1. The escape latency of the rats in the Morris water maze. After a systemic single injection of KA, Water maze task to find a hidden platform was performed for 4 days. In day 5, the platform was removed to evaluate the spatial memory ability, with saline-treated rats as the naive control group. Values were the mean ± SEM of the mean escape latency of four trials per day. Rats treated KA with SRS (■, $n = 19$) were unable to acquire the spatial learning memory task as rapidly as KA rats without SRS (▒, $n = 16$) and saline-treated group (□, $n = 16$) significantly in days 1, 2, 3, 4, and 5 (**$P < 0.01$), respectively. In addition, there was no difference in KA group without SRS and saline-treated group.

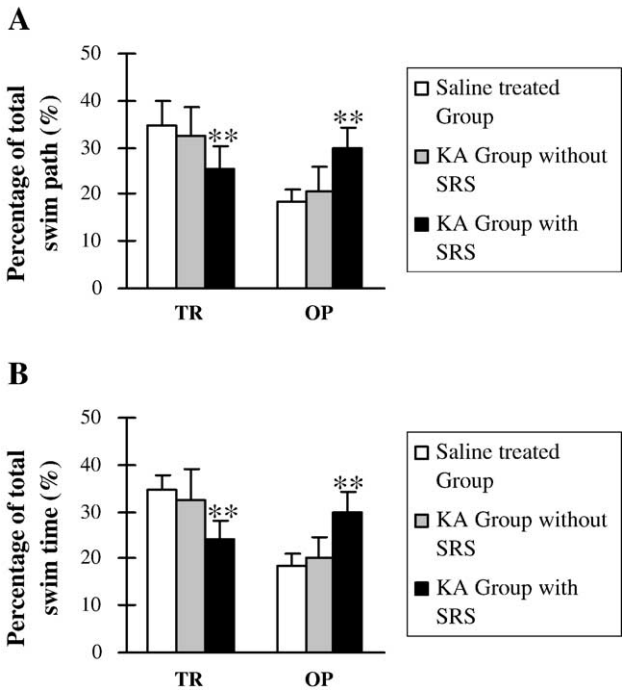

Fig. 2. (A) The swim path spent in the quadrants of the rats in Morris water maze. Probe tests were given in day 5 of water maze testing. Memory performance of individual rats was expressed as the percentage of swim path spent in the training quadrant (TR) and opposite quadrant (OP). Compared with the KA-treated group without SRS ($n = 16$, gray bars) and saline-treated group ($n = 16$, white bars), KA-treated rats with SRS ($n = 19$, black bars) spent less swim path in the TR (**$P < 0.01$) and more swim path in the OP (**$P < 0.01$). There was no difference between the swim path spent in the TR and OP for the KA-treated rats with SRS. (B) The time spent in the quadrant of the rats in Morris water maze. Probe tests were given in day 5 of water maze testing. Memory performance of individual rats was expressed as percentage of time spent in TR and OP. The data presented the mean ± SEM percentage of time spent in the TR and OP. Compared with the KA-treated group without SRS ($n = 16$, gray bars) and saline-treated group ($n = 16$, white bars), KA-treated rats with SRS ($n = 19$, black bars) spent less time in TR (**$P < 0.01$) and more time in OP (**$P < 0.01$).

2.6. Statistical analysis

All data were expressed as mean ± SEM. Differences between groups were assessed using an ANOVA with post hoc test of LSD in Equar Variances Assumed. In all comparisons, statistical significance was set at $P < 0.05$.

Table 1
The number of platform crossings in the rats

Group	Platform crossings
Saline-treated group	2.38 ± 0.89
KA group without SRS	2.06 ± 1.34
KA group with SRS	0.25 ± 0.56**

In the probe test, KA-treated group with SRS ($n = 19$) crossed the location of platform less than the KA-treated group without SRS ($n = 16$) and saline-treated group ($n = 16$) (**$P < 0.05$). Values are the mean ± SEM of number of platform crossings.

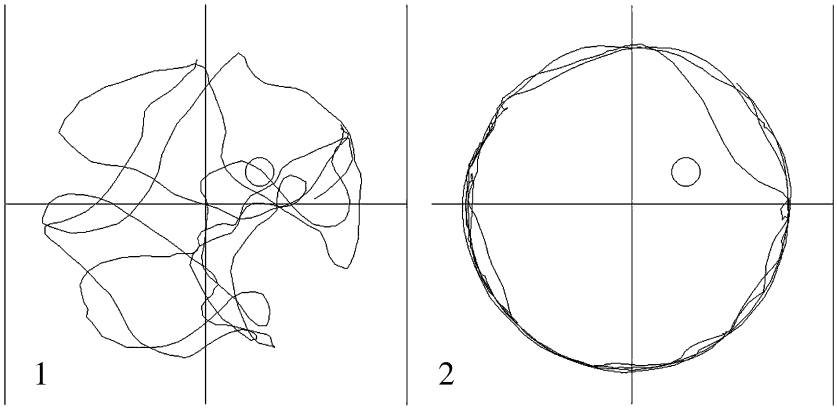

Fig. 3. The search strategy of KA-treated rats with and without SRS in Morris water maze. (1) Representative probe trial of a KA-treated rat without SRS. The swim path trace shown here provided an excellent example of a selective search. During the probe trial, this rat spent 44% of the time in the correct quadrant (vs. 14% in the opposite quadrant) and crossed the exact area where the platform had been five times. (2) Representative probe trial of a KA-treated rat with SRS. This trace represented a circling strategy. During the probe trial, the rat didn't cross the position of platform and spent 17% of the time in this quadrant (vs. 31% in the opposite quadrant).

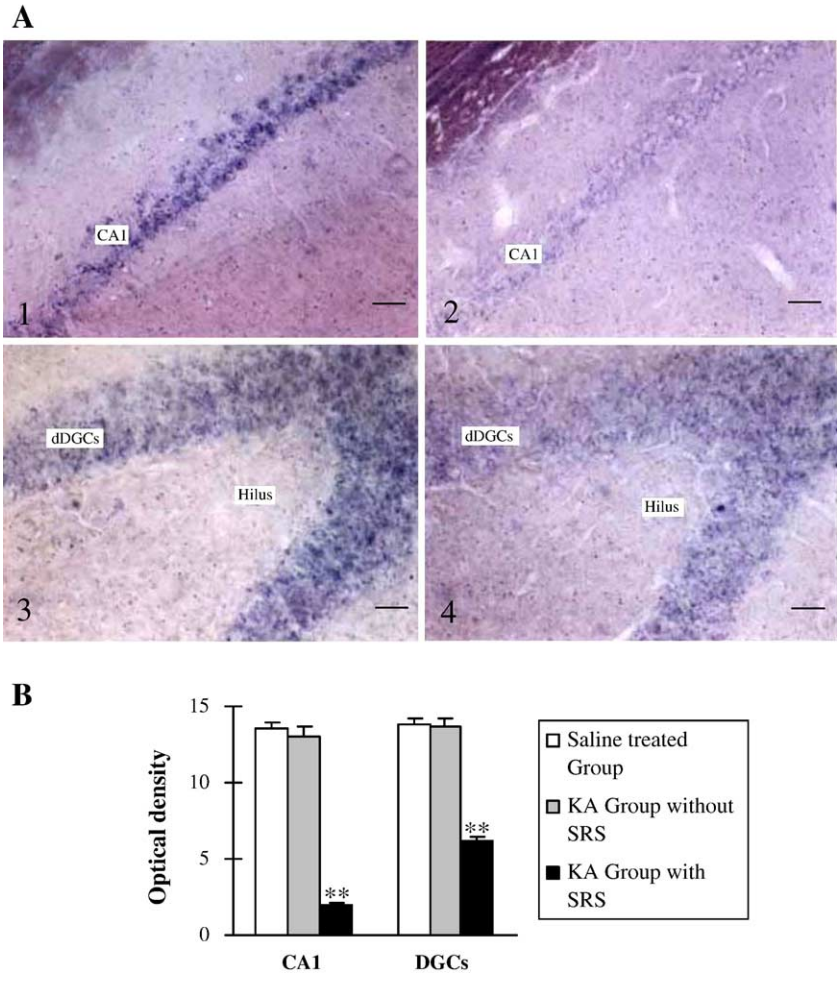

Fig. 4. In situ hybridization of *ERG1/NSF* mRNA expression in the hippocampus of the rats. (A). The *ERG1/NSF* mRNA expression in the hippocampus of the rats. (1) CA1 area in the KA-treated rats without SRS, (2) CA1 area in the KA-treated rats with SRS, (3) dDGCs in the KA-treated rats without SRS, (4) dDGCs in the KA-treated rats with SRS. Scale bars are 100 μm. (B) The optical density of *ERG1/NSF* mRNA expression in the hippocampus of the rats. Compared with the KA-treated group without SRS (gray bars, $n = 4$) and saline-treated group (white bars, $n = 4$), there was a significant decrease of *ERG1/NSF* mRNA expression in CA1 (**$P < 0.01$) and dDGCs (**$P < 0.01$) in KA group with SRS (black bars, $n = 4$). Data presented are mean ± SEM.

3. Results

3.1. The seizure scale in KA-treated rats

According to the scale of Racine, all KA-treated rats were in the stages from 4 to 5. 3 weeks later, 19 KA-treated rats developed SRS and were regarded as the experiment group, while 16 KA-treated rats did not develop SRS and were regarded as the experimental control group. Saline-treated rats were regarded as the naive control group.

3.2. Morris water maze

During 5 days of formal testing, escape latency of KA group with SRS was always much longer than that of the KA group without SRS ($P < 0.01$; Fig. 1) and saline-treated group ($P < 0.01$), respectively. No difference was found between KA group without SRS and saline-treated group. In KA group with SRS, escape latency did not decrease since day 1, indicating its learning memory disability.

To confirm the lack of spatial memory in the KA group with SRS, we conducted probe test and measured the percentage of swim length and time spent in the training quadrant (TR) and opposite quadrant (OP). An animal that has learned the location of the platform should spend longer time in the TR than any other quadrants. Compared to KA group without SRS and saline-treated group, KA group with SRS spent less length and time in the TR but more length and time in the OP ($P < 0.01$; Fig. 2 with representative traces shown in Fig. 3). Furthermore, KA-treated group with SRS crossed the location of platform much less than the KA-treated group without SRS and saline-treated group. ($P < 0.05$; Table 1). These data indicate a spatial memory disability in KA-treated rats with SRS.

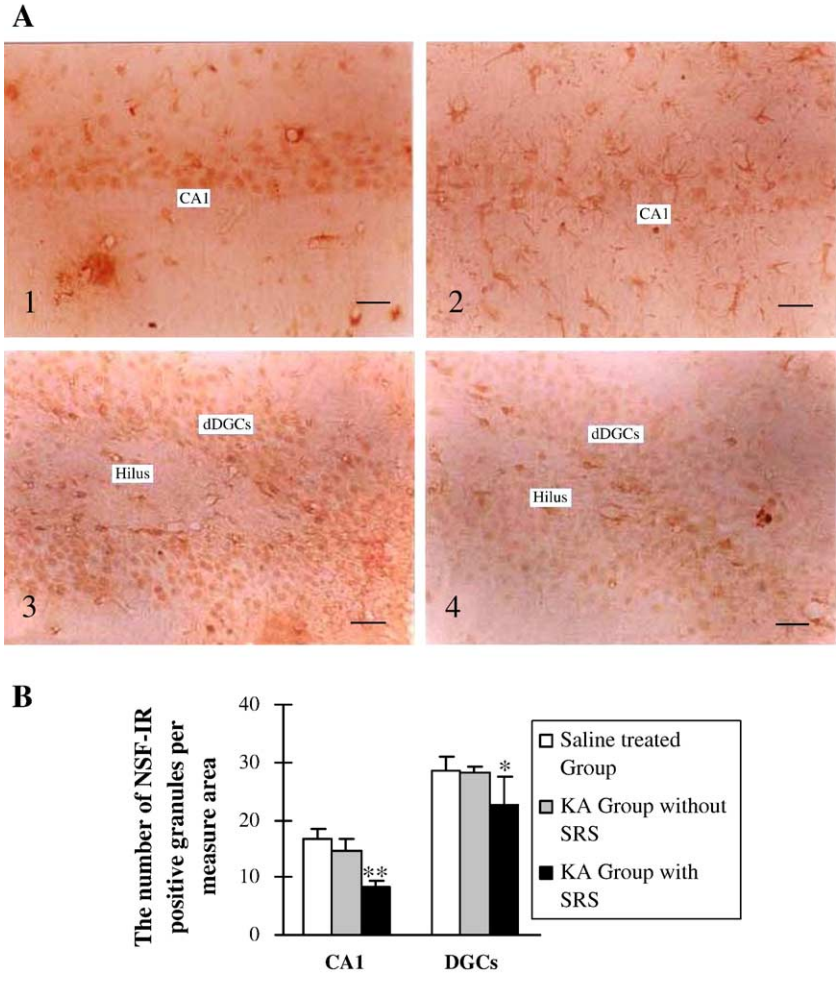

Fig. 5. Immunohistochemistry of NSF in the hippocampus of the rats. (A) The NSF immunoreactive granules by DAB staining in the hippocampus of the rats. (1) CA1 area in the KA-treated rats without SRS, (2) CA1 area in the KA-treated rats with SRS, (3) dDGCs in the KA-treated rats without SRS, (4) dDGCs in the KA-treated rats with SRS. Scale bars are 100 μm. (B) The number of NSF immunoreactive granules in the hippocampus of the rats. Compared with the KA-treated group without SRS (gray bars, $n = 4$) and saline-treated group (white bars, $n = 4$), there was a significant decrease of NSF immunoreactive granules in CA1 (**$P < 0.01$) and dDGCs (*$P < 0.05$) in KA-treated rats with SRS (black bars, $n = 4$). There was no difference in KA-treated group without SRS and saline-treated group. Bars represented mean number ± SEM of neurons. Measure area was 3120.4 μm^2 (43.1 μm × 72.4 μm, 3.3 × 20), the average of four positions was selected to be analyzed.

3.3. In situ hybridization

After Morris water maze, the rats were measured for *ERG1/NSF* mRNA expression in the brain. Compared with KA group without SRS and saline-treated group, KA group with SRS showed reduced level of *ERG1/NSF* mRNA in CA1 and dorsal dentate gyrus cells (dDGCs) of the hippocampus ($P < 0.01$; Fig. 4).

3.4. Immunohistochemistry

3.4.1. The effects of KA on the NSF immunoreactive granules in the hippocampus

After Morris water maze, the rats were measured for NSF immunoreactive granules in the brain. Compared with KA group without SRS and saline-treated group, KA group with SRS showed reduced NSF immunoreactive granules in CA1 and dDGCs of the hippocampus ($P < 0.01$ and $P < 0.05$, respectively; Fig. 5), similar to the in situ hybridization result.

3.4.2. The effects of KA on the DA neurons in the ventral tegmental area (VTA)

After Morris water maze, the rats were measured for TH immunoreactive DA neurons. Compared with KA group without SRS and saline-treated group, KA group with SRS showed a largely reduced number of TH immunoreactive DA neurons in VTA ($P < 0.01$; Fig. 6).

4. Discussion

It has been reported that systemic KA-treated rats with SRS performed poorer in water maze and spatial bias testing [32]. However, the mechanism is unknown. In the study, we first confirmed the behavioral deficits in KA-treated rats with SRS and then investigated the molecular mechanisms underlying these deficits.

First, we treated rats with a single injection of KA (10 mg/kg, s.c.) to induce seizure. During the following 3 weeks, the rats that developed SRS were used as TLE model. In water maze, the KA-treated rats with SRS exhibited significantly poorer acquisition of spatial learning memory than the rats without SRS. The KA-treated rats with SRS displayed no difference in escape latency among days 4, 3, 2, and 1, indicating no improvement of learning. Spatial probe test further demonstrated that the number of platform crossings in the KA-treated rats with SRS were lower than that of the rats without SRS. Meanwhile, the KA-treated rats with SRS spent less length and time in the TR but more length and time in the OP. These data demonstrate spatial learning memory deficits in KA-treated rats with SRS and suggest that SRS impairs spatial learning memory.

To identify the underlying mechanism for these learning memory deficits, we studied the expression pattern of *ERG1/NSF* in KA-treated rats with SRS. We found that the levels of *ERG1/NSF* mRNA and NSF protein were down-regulated in the CA1 and dDGCs of the hippo-

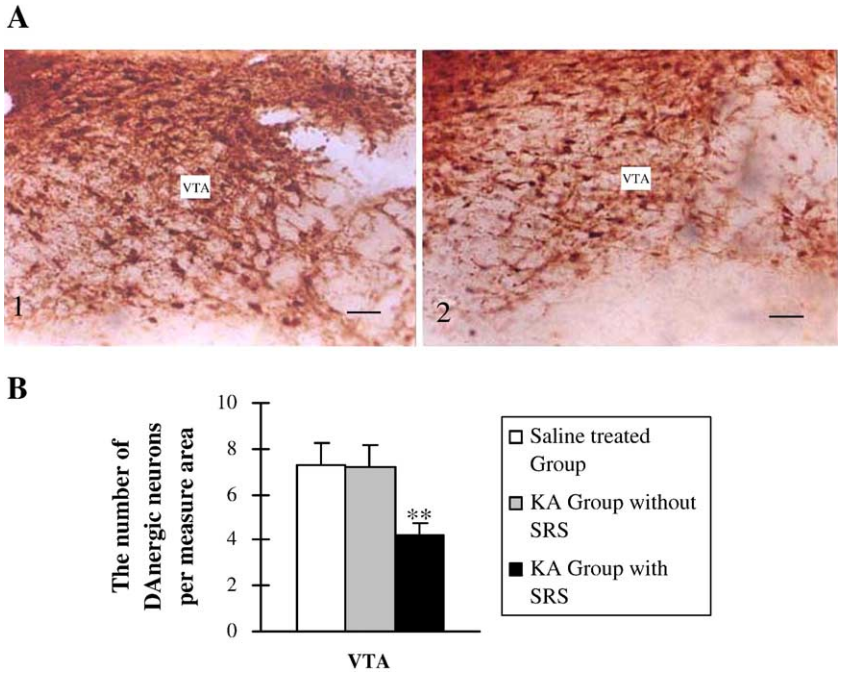

Fig. 6. Immunohistochemistry analysis of TH immunoreactive DA neurons in the VTA of the rats. (A) DA neurons in the VTA of the rats. (1) VTA of the KA-treated group without SRS, (2) VTA of the KA-treated group with SRS. Scale bars are 100 μm. (B) The number of DA neurons in the VTA of the rats. Quantitatively compared with the number of DA neuron survival in the saline-treated rats ($n = 4$, white bars) and KA-treated group without SRS ($n = 4$, gray bars), KA-treated group with SRS ($n = 4$, black bars) showed a large loss of DA neurons in VTA (**$P < 0.01$). Bars represented mean number ± SEM of neurons. Measure area was 3120.4 μm^2 (43.1 μm × 72.4 μm, 3.3 × 20). The average of four locations selected was to be analyzed.

campus. The hippocampus has been known to play a critical role in certain types of learning, including spatial learning [13,26]. Specific cells within the hippocampus become selectively activated when an animal is placed in particular locations within its environment [37]. Rats display dysfunctions in spatial memory when various sites within the hippocampus are lesioned [33]. Within the hippocampus, DGCs serve to restrict or amplify signals that originate in extra hippocampal sites and propagate into the hippocampus properly [23]. The CA1 region of hippocampus plays significant roles in associational memories [36,39]. NSF, an ATPase, is an essential component of various membrane fusion events including the exocytosis of synaptic vesicles, whose activity is required to disassemble the associated soluble NSF attachment protein receptor (SNARE) complex [14,17,35]. NSF has also been identified as a postsynaptic protein that interacts with the glutamate receptor 2, α amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor subunit [27,31]. This interaction has been shown to rapidly regulate AMPA receptor function at synapses [16,24,25,27,31] and plays a role in hippocampal long-term potentiation (LTP) [6,20] and long-term depression (LTD) [16,24,25]. Recent data showed that NSF expression decreased significantly in the hippocampus of two mouse lines with learning deficits, namely, the neural nitric oxide synthase (nNOS) knockout mice [15] and the transgenic mice overexpressing superoxide dismutase 1(SOD1) [30]. These results, together with ours, suggest that down-regulation of *ERG1*/NSF in the hippocampus, which would alter glutamate receptor 2 function and consequently LTP/LTD, might underlie the spatial learning impairment induced by SRS.

As an extension of our study on the KA epilepsy model, we examined the effect of KA on DA neurons. Interestingly, we found a large loss of TH immunoreactive DA neurons in ventral tegmental area (VTA) of the KA-treated rats with SRS. Recent evidence suggests a close relationship between memory formation in the hippocampus and dopaminergic neuromodulation originated in the VTA [29,38]. Rats with mesohippocampal DA lesion are significantly impaired in the retention of spatial information [9,10], whereas dopamine agonists, in aged animals, can promote hippocampus-dependent learning [2]. Taken together, our data suggest that the loss of DA neuron in VTA might contribute to the learning deficits by disrupting the integrity of VTA–hippocampal DA pathway.

In summary, we found reduced mRNA and protein levels of NSF in CA1 and DGCs and a large loss of TH immunoreactive DA neurons in VTA in KA-treated rats with SRS, which also exhibited impaired spatial learning memory. Our study suggested that: first, SRS impairs spatial learning; secondly, these deficits might attribute to the reduced level of *ERG1*/NSF; and finally, SRS alters the VTA–hippocampal DA pathway, which contribute to SRS-induced learning memory deficits. Future research should explore the role of *ERG1*/NSF in neuropathology and neurochemistry of cognition dysfunction in TLE using NSF knockout animals, as well as the role of the VTA–hippocampal DA pathway in SRS-induced learning memory deficits.

Acknowledgments

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