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Research paper

Salidroside protects against kainic acid-induced status epilepticus *via* suppressing oxidative stress

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HIGHLIGHTS

- The effect of salidroside in kainic acid induced-status epilepticus is reported for the first time.
- Salidroside protects against kainic acid induced-status epilepticus *via* suppressing oxidative stress.
- The AMPK/SIRT1/FoxO1 pathway may mediate the neuroprotection of salidroside.

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ABSTRACT

There are numerous mechanisms by which the brain generates seizures. It is well known that oxidative stress plays a pivotal role in status epilepticus (SE). Salidroside (SDS) extracted from *Rhodiola rosea* L. shows multiple bioactive properties, such as neuroprotection and antioxidant activity *in vitro* and *in vivo*. This study explored the role of SDS in kainic acid (KA)-induced SE and investigated the underlying mechanism. Latency to SE increased in the SDS-pretreated mice compared to the KA group, while the percentage of incidence of SE was significantly reduced. These results suggested that pretreatment with SDS not only delayed SE, but it also decreased the incidence of SE induced by KA. KA increased MDA level and reduced the production of SOD and GSH at multiple timepoints after KA administration. SDS inhibited the change of MDA, SOD and GSH induced by KA prior to SE onset, indicating that SDS protects against KA-induced SE *via* suppressing oxidative stress. Based on these results, we investigated the possible molecular mechanism of SDS. Pretreatment with SDS reversed the KA-induced decrease in AMP-activated protein kinase (AMPK); increased the sirtuin 1 (SIRT1) deacetylase activity in KA-treated mice, which had no demonstrable effect on SIRT1 mRNA and protein; and suppressed the KA-induced increase in Ace-FoxO1. These results showed that AMPK/SIRT1/FoxO1 signaling is possibly the molecular mechanism of neuroprotection by SDS.

1. Introduction

Epilepsy, one of the most common neurological diseases, is characterized by recurrent epileptic episodes and can lead to morbidity. It affects approximately 1% of the population worldwide. As the most severe form of an epileptic seizure, status epilepticus (SE) is refractory to medical therapy, and it has a high mortality [1]. Kainic acid (KA), an analog of glutamate, has been widely used as a tool for the induction of experimental temporal lobe epilepsy in rodents [2]. A single systemic injection of KA at a convulsive dose produces limbic status epilepticus, followed by long-term spontaneous recurrent seizures (SRS). Currently, most patients take antiepileptic drugs (AEDs); however, AEDs are ineffective or exert intolerable adverse effects in approximately one third of epilepsy patients. Therefore, it is necessary to explore new compounds to ameliorate seizures and eliminate adverse side effects.

The underlying mechanisms of SE are not well understood. Cumulative evidence suggests that oxidative stress may play an important role in acute seizures. Oxidative stress is defined as an imbalance between free radicals and antioxidant defense mechanisms in a biological system. Malondialdehyde (MDA) reflects the state of the free radical system. Free radical scavengers, such as super oxide dismutase (SOD) and reduced glutathione (GSH), protect against oxidative damage [3]. Thus, antioxidants may have a potential role in preventing the development of epilepsy. Salidroside (SDS), the major active component of *Rhodiola rosea* L., displays various biological activities, including anti-hypoxic, anti-aging, anti-aging, anti-tumor [4], anti-inflammation, cardioprotective and

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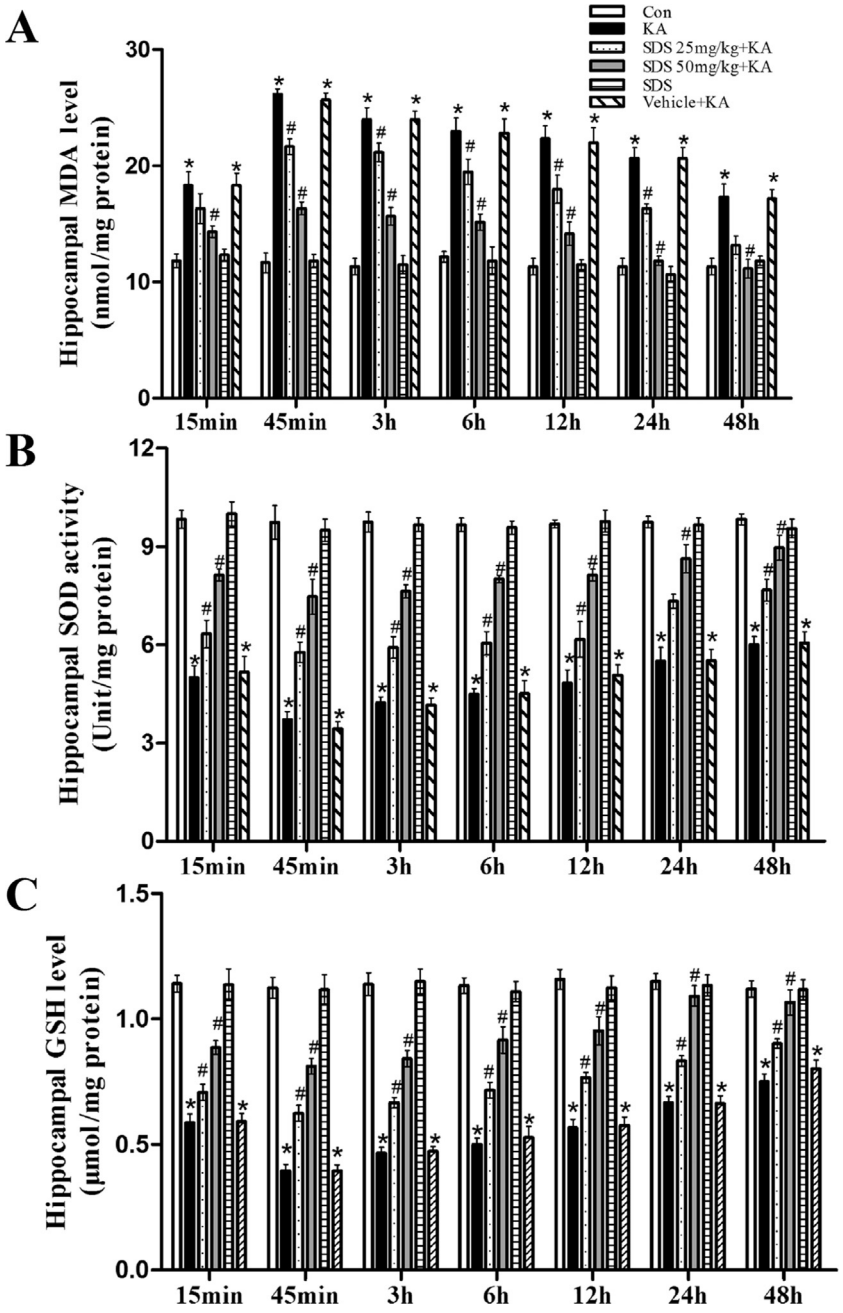

Fig. 1. Effect of SDS on MDA, SOD and GSH in KA-treated mice. Mice were sacrificed at different time points after KA injection, and the MDA level (A), SOD activity (B) and GSH level (C) were analyzed. Data are expressed as the mean ± SEM (n = 5–6 mice/group). ($^{*}P < 0.05$ *vs* Con at the same timepoint; $^{\#}P < 0.05$ *vs* KA or Vehicle + KA at the same timepoint).

neuroprotective effects [5]. It has been shown that SDS is protective against oxidative stress *in vitro* and *in vivo* [6,7]. Moreover, previous studies have demonstrated that SDS rapidly crosses the blood brain barrier (BBB) [8,9] and exhibits beneficial effects in animal models of cerebral ischemic injury [10], vascular dementia [5] and Alzheimer's disease [11]. Nevertheless, little evidence exists demonstrating the role of SDS in epilepsy. Therefore, in this study, we investigated whether SDS exerted a protective effect on KA-induced SE through suppressing oxidative stress.

It has been shown that AMP-activated protein kinase (AMPK) is neuroprotective against SE-induced brain damage, and SDS protects cardiomyocytes from oxidative stress by activating AMPK [12]. Silent information regulator 1 (SIRT1) enhances the antioxidant system in SE [13]. It has been reported that SIRT1 plays an important role in SDS-mediated neuroprotection during hypoxia [9]. In addition, the AMPK/SIRT1 pathway is involved in the protective effect of SDS against oxidative stress in neuroblastoma and human umbilical vein endothelial cells [14], which raises the interesting possibility that SDS protects against oxidative damage in SE *via* the AMPK/SIRT1 pathway. As a member of the forkhead box O (FoxO) transcription factors, FoxO1 plays an important role in cell survival by transactivating reactive oxygen species (ROS)-detoxifying enzymes such as superoxide dismutase 2 (SOD2/MnSOD) and catalase. It has also been proposed that SIRT1 promotes the expression of FoxO target genes involved in stress resistance. Thus, SIRT1 appears to shift the FoxO1-dependent response away from cell death and toward oxidative