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PROTECTION AGAINST COGNITIVE IMPAIRMENT AND MODIFICATION OF EPILEPTOGENESIS WITH CURCUMIN IN A POST-STATUS EPILEPTICUS MODEL OF TEMPORAL LOBE EPILEPSY

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Abstract—Epileptogenesis is a dynamic process initiated by insults to the brain that is characterized by progressive functional and structural alterations in certain cerebral regions, leading to the appearance of spontaneous recurrent seizures. Within the duration of the trauma to the brain and the appearance of spontaneous recurrent seizures, there is typically a latent period, which may offer a therapeutic window for preventing the emergence of epilepsy. Previous animal studies have shown that curcumin can attenuate acute seizure severity and brain oxidative stress, but the effect of curcumin on epileptogenesis has not been studied. We examined the effect of continued administration of curcumin during the latent period on epileptogenesis and the deleterious consequences of status epilepticus in adult rats in a post-status epilepticus model of temporal lobe epilepsy induced by kainic acid. We demonstrate that, while administration of curcumin treatment during the latent period does not prevent occurrence of spontaneous recurrent seizures after status epilepticus, it can attenuate the severity of spontaneous recurrent seizures and protect against cognitive impairment. Thus, treatment with curcumin during the latent period following status epilepticus is beneficial in modifying epileptogenesis.

Key words: curcumin, epileptogenesis, kainic acid, temporal lobe epilepsy, status epilepticus.

INTRODUCTION

Epilepsy is a chronic neurological disease, characterized by spontaneous recurrent seizures (SRS), affecting 1% of the world's population (Bell and Sander, 2001). Temporal lobe epilepsy (TLE), the most common type of refractory partial epilepsy in adults, possesses pathological features which include hippocampal sclerosis (i.e. neuronal loss and gliosis) and neuronal network alterations in the hippocampal formation. TLE often develops many years after an initial precipitating injury (IPI) to the brain such as traumatic brain injury, stroke, central nervous system infection, brain tumor, febrile seizure and status epilepticus (SE) (Herman, 2002). Despite the increasing number of antiepileptic drugs (AEDs) developed in recent years, up to 30% of patients with TLE are pharmaco-resistant (Schuele and Luders, 2008). Surgical resection of the epileptic focus is a treatment option for patients with TLE who are pharmaco-resistant, however, this procedure itself can lead to severe adverse complications such as cognitive impairment (Heller et al., 2009). Untreated epileptic seizures can also lead to subsequent brain injury, causing cognitive impairment that affect quality of life as accumulated damage results in social dysfunction. The treatment of epilepsy concentrates particularly on the prevention or suppression of epileptic seizures, which is ultimately the product of the epileptogenesis (i.e. the development of SRS) (Walker et al., 2002). The treatment goal is to avoid the development of epilepsy by preventing or reversing epileptogenesis in patients that are at risk of developing epilepsy after an IPI.

Epileptogenesis represents a critical period for epilepsy development (Giblin and Blumenfeld, 2010). It is a dynamic process initiated by an IPI that is character-

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Abbrevitations: AEDs, antiepileptic drugs; ANOVA, analysis of variance; BBB, blood–brain barrier; DG, dentate gyrus; DH, dentate hilus; EEG, electroencephalogram; ELISA, enzyme-linked immunosorbent assay; GFAP, glial fibrillary acidic protein; IL-1β, interleukin-1β; IPI, initial precipitating injury; KA, kainic acid; MFS, mossy fiber sprouting; MWM, Morris water maze; PFA, paraformaldehyde; SE, status epilepticus; SRS, spontaneous recurrent seizures; TLE, temporal lobe epilepsy; TNF-α, tumor necrosis factor-α.

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ized by progressive functional and structural alterations in certain cerebral regions and leads to the appearance of SRS. Once the SRS has occurred, the epileptogenic process may be well established and difficult to intervene. Disruption of the process before the appearance of SRS, could prevent development of epilepsy in patients at risk or increase the potential for a better long-term prognosis. Between the IPI and the appearance of SRS, there is typically a latent period, which may offer a therapeutic window to prevent or modify epileptogenesis (Walker et al., 2002; Dichter, 2009; White and Loscher, 2014). Up until now, the exact underlying mechanisms of epileptogenesis have not been well defined. Some changes (such as the inflammation cascade, neuronal loss, gliosis, mossy fiber sprouting (MFS), etc.) have been implicated in epileptogenesis, providing interesting targets for antiepileptogenesis or disease modification (Dudek et al., 2002; Pitkanen and Lukasiuk, 2011; Sendrowski and Sobaniec, 2013; Pitkanen and Engel, 2014). Pharmacological interventions during the latent period can modify disease effects on epileptogenesis (Pitkanen et al., 2004). Current AEDs provide only symptomatic suppression of seizures without preventing epileptogenesis or altering the long-term detrimental effects of SE (Rogawski and Loscher, 2004), and they also possess multiple adverse effects. Research focused on the therapeutic modification of seizure-induced molecular and cellular responses provides new opportunities for intervention beyond simply seizure suppression (Pitkanen and Sutula, 2002). Therefore, there is a pressing need to develop effective alternative therapies that completely or partially prevent the emergence of SRS after an IPI and that alter the long-term detrimental effects of SE by preventing or reducing deleterious changes that occur during the epileptogenic process (Kobow et al., 2012).

Curcumin is the active component of turmeric which is derived from the rhizome of Curcuma Longa. Previous studies have suggested that curcumin has a variety of pharmacologic effects such as antioxiding, anti-inflammatory, anti-amyloid, anticancer and so on (Zhou et al., 2011). Curcumin is nontoxic and can penetrate the blood–brain barrier (BBB). Curcumin has been proven to exhibit activity against various neurologic diseases and is effective against memory deficit, oxidative stress, and neuronal damage.

There is compelling evidence that natural compounds with antioxidant properties can contribute to the prevention of seizure-induced pathology (Ambrogini et al., 2014). Among these compounds, curcumin was shown to play a beneficial role in epilepsy by attenuating acute seizure severity and brain oxidative stress mainly due to its antioxidant properties. Scientific studies have demonstrated that curcumin pretreatment significantly reduces astrocytic activation, neuronal cell death and oxidative stress in the hippocampus, which in turn ameliorates the long-term consequences of SE. This mechanism was termed ‘‘initial insult modification” rather than ‘‘true antiepileptogenesis or disease-modifying effects”. To date, however, published literature is lacking on whether continued administration of curcumin after SE has an effect on epileptogenesis in the animal model of TLE. Only a drug with the ability to prevent epilepsy after an IPI such as SE would be clinically relevant (Loscher, 2002). From a therapeutic point of view, continued administration of neuroprotectants should be necessary in the treatment of brain injury induced by SE (Nairismagi et al., 2004). There is a limited time for drugs to intervene in the epileptogenesis process, which requires the earliest intervention possible.

The current study was designed to investigate the effect of continued administration of curcumin after SE on epileptogenesis and the deleterious consequences of SE in a post-status epilepticus model of TLE induced by kainic acid (KA).

EXPERIMENTAL PROCEDURES

Animals

Adult male Wistar rats (220–250 g), provided by the Animal Center of Jilin University (China), were housed under standard laboratory conditions (22–25 °C, 50–60% humidity, and a 12:12-h light:dark cycle) with food and water available *ad libitum*. They were acclimatized for at least one week before any manipulations. All experimental protocols were approved by the Ethics Committee of the First Clinical College of Harbin Medical University and confirmed to the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH publications No. 80-23, revised 1996). All efforts were made to minimize animal suffering and reduce the number of animals used.

Experimental design

Rats were randomly divided into three groups. (1) SE + curcumin: SE was induced in rats with an intrahippocampal KA injection, followed 0.5 h after SE cessation by an intraperitoneal (i.p.) injection of 100 mg/kg curcumin (Sigma) dissolved in 5 N NaOH and titrated to pH 7.4 using 1 N HCl and diluted with physiological saline (Zhao et al., 2010); this curcumin injection was repeated once daily for 14 consecutive days. (2) SE:SE was induced in rats with an intrahippocampal KA injection followed by i.p. injection of saline at 0.5 h after SE cessation, repeated once daily for 14 consecutive days. (3) Control: rats were subjected to intrahippocampal saline injection, followed by i.p. injection of saline once daily for 14 days. The experimental protocol is illustrated in Fig. 1.

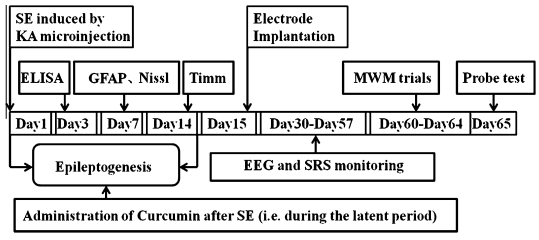

Fig. 1. Schematic illustration of the experimental schedule performed in this study. SRS = spontaneous recurrent seizures, MWM = Morris water maze.