Altered expression of adrenocorticotropic hormone in the epileptic gerbil hippocampus following spontaneous seizure

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INTRODUCTION

Individuals are continuously exposed to potential disturbances (stressors) to equilibrium of essential body functions. In general, stress is among the most frequently self-reported precipitant of seizures in patients with epilepsy (1-3). This leads to activation of the hypothalamo-pituitary-adrenal (HPA) axis. The initial step in this process is elevation of corticotrophin-releasing factor (CRF) in response to input from extrahypothalamic sources. This release, in turn, causes the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary into the circulation, which subsequently leads to release of corticosteroid hormones (cortisol in humans, corticosterone in rodents) from the adrenal cortex. Biochemically, there is evidence that cortisol plays a role in seizure control (4). In addition, a role of stress hormones in the control of epilepsy has shown predisposition to the development and/or progression of epilepsy (5, 6). Moreover, glucocorticoids, ACTH, and steroid manipulations have been shown to be effective in the management of pediatric epilepsies (7, 8).

Mongolian gerbils are good models for studies of genetic epilepsy because this animal offers genetic control, breeding proclivity, and an ease of behavioral testing (9, 10). The seizures exhibited by gerbils are consistent over time, so it is possible to correlate seizure intensity records with morphological observations (9, 11-13). Previous studies have focused on the role of CRF, the regulator of pituitary ACTH release, in epileptic mechanisms (16, 17). However, it has also been recently reported that adrenal glucocorticoid hormones have a potent effect on hyperexcitatory neuronal damage of pyramidal neurons in CA1 (18). In addition, potent anticonvulsant effects of ACTH have been reported in Mongolian gerbils (19). Although the ACTH level increases in temporal lobe epilepsy patient, it is unknown whether expressions of ACTH are altered depending on the time course following spontaneous seizure onset in the hippocampus of epileptic Mongolian gerbils. Therefore, we investigated the temporal and spatial alterations of ACTH immunoreactivity in the hippocampus of epileptic Mongolian gerbils. Therefore, we investigated the temporal and spatial alterations of ACTH immunoreactivity in the hippocampus of epileptic Mongolian gerbils. Therefore, we investigated the temporal and spatial alterations of ACTH immunoreactivity in the hippocampus of epileptic Mongolian gerbils. Therefore, we investigated the temporal and spatial alterations of ACTH immunoreactivity in the hippocampus of epileptic Mongolian gerbils.

RESULTS AND DISCUSSION

Altered expression of ACTH in the epileptic gerbil hippocampus

As shown in Fig. 1, ACTH immunoreactivity was rarely observed in any hippocampal region in the SR gerbil hippocampus (Fig. 1A, 1E, 1F, 2A1, 3A1, and 4A). However, in the pre-seizure SS gerbil hippocampus, ACTH immunoreactivity was detected in all hippocampal regions (Fig. 1B, 1E, and 1F). Briefly, ACTH immunoreactive neurons, which were presumed by morphological and distributional patterns to be interneurons, were distinctly identified in the CA1, subiculum, and dentate hilar regions (Fig. 2A2, 3A2, and 4B). In addition, the immunoblot study for the ACTH levels in the hippocampus and quantitative analyses for the average cell numbers of ACTH-positive neurons revealed its expression in all hippocampal regions (Fig. 1E, 1F, 2B, 3B, and 4E).
In this study, spatial distributions of ACTH immunoreactive neurons were observed chronologically in the pre-seizure SS gerbil hippocampus compared to the SR gerbil groups. This result indicates that ACTH may modulate seizure activity in the epileptic gerbil hippocampus. To be more specific, altered ACTH expression of the pre-seizure SS gerbil group may be indicative of the hyperexcitable state of the hippocampus for seizure onset. Many research groups reported that ACTH possesses neurotrophic effects in the peripheral and central nervous system during both development and regeneration (20, 21). Thus, ACTH may influence the hyperexcitable state of the epileptic gerbil hippocampus. In addition, the significant enhancement of glucocorticoid immunoreactivities in the pre-seizure SS gerbil hippocampus compared to SR gerbils has been described (22). Glucocorticoids secreted from the adrenal glands are important in maintaining granule cell survival and structural integrity of the granule cell layer in the hippocampus, because the ACTH peptide may be the final common mediator to protect from hyperexcitatory neuronal death following glucocorticoid inhibition (21). Moreover, selective ACTH expression may play an important role in the neurodegenerative process, influencing microglia and neurons and injection of the ACTH analog to protect CA1 pyramidal neurons from neuronal damage (18). The previous and present results collectively support the notion that enhanced ACTH immunoreactivities in the pre-seizure SS gerbil hippocampus may be indicative of the hyperexcitatory neuronal state of epileptic hippocampus, showing a lower threshold for seizure initiation.

As shown in Fig. 2 and 3, the double immunofluorescence