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Comorbidity between epilepsy and depression: Role of hippocampal interleukin-1β

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ABSTRACT

Depression is a frequent comorbidity of temporal lobe epilepsy (TLE); however, its mechanisms remain poorly understood and effective therapies are lacking. Augmentation of hippocampal interleukin-1β (IL-1β) signaling may be a mechanistic factor of both TLE and clinical depression. We examined whether pharmacological blockade of hippocampal interleukin-1 receptor exerts antidepressant effects in an animal model of comorbidity between TLE and depression, which developed in Wistar rats following pilocarpine status epilepticus (SE). In post-SE animals, depression-like state was characterized by behavioral equivalents of anhedonia and despair; dysregulation of the hypothalamo–pituitary–adrenocortical axis; compromised raphe–hippocampal serotonergic transmission. Two-week long bilateral intrahippocampal infusion of human recombinant Interleukin-1 receptor antagonist (IL-1ra) improved all of the examined depressive impairments, without modifying spontaneous seizure frequency and without affecting normal parameters in naïve rats. These findings implicate hippocampal IL-1β in epilepsy-associated depression and provide a rationale for the introduction of IL-1β blockers in the treatment of depression in TLE.

Introduction

Depression represents one of the most common comorbidities of temporal lobe epilepsy (TLE) and has profound negative impact on the quality of life of TLE patients (Kanner, 2003; Kondziella et al., 2007). However, the causes and mechanisms of depression in TLE remain poorly understood, partly due to the lack of proper animal models. We previously reported that rats which develop chronic epilepsy following pilocarpine status epilepticus (SE) exhibited set of interictal disorders congruent with depression. Specifically, the following depressive impairments were documented in post-SE animals: behavioral equivalents of anhedonia (i.e. loss of the ability to experience pleasure) and despair; dysregulation of hypothalamo–pituitary–adrenocortical (HPA) axis; and compromised raphe–hippocampal serotonergic transmission (Mazarati et al., 2008, 2009a). As the pilocarpine model reproduces both epileptic and depressive states, it may serve as a model of comorbidity between TLE and depression and as such, can be used both for studying mechanisms of this condition and as a screening platform for therapeutic interventions. Since depression is a multisymptomatic and a multifactorial disorder, further studies are necessary to advance the validation of this model; however, the impairments established up to date allow initial experimental therapy studies.

One factor which may contribute to depression in TLE is hippocampal tissue inflammation and, particularly, enhanced interleukin-1β (IL-1β) signaling. Indeed, activation of hippocampal IL-1β and its receptor (IL-1R) has been an established hallmark of TLE both in clinical and experimental settings and has been implicated in mechanisms of epileptogenesis (Bartfai et al., 2007; Ravizza et al., 2008; Vezzani et al., 2002, 2008; Vezzani and Granata, 2005). At the same time, IL-1β and other inflammatory cytokines may lead to depression conceivably via inducing perturbation in the HPA axis, as suggested by clinical observations, and confirmed by experimental studies (Capuron and Dantzer, 2003; Dunn et al., 2005; Leonard, 2006). Particularly, the dysregulation of the HPA axis (which represents a neuroendocrine hallmark of depression; Kondziella et al., 2007; Swaab et al., 2005) can be induced by the direct activation of hippocampal IL-1β signaling (Melik Parsadaniantz et al., 1999).

Such connections between epilepsy and IL-1β on the one hand and IL-1β and depression on the other hand prompted us to examine whether protracted pharmacological blockade of hippocampal IL-1R exerts antidepressant effect in the post-SE model of comorbidity between epilepsy and depression.

Methods

Subjects

The experiments were performed in male Wistar rats (Charles River, Wilmington, MA), 50 days old at the beginning of the study, in accordance with the policies of the National Institutes of Health.

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Study design is outlined in Fig. 1. Detailed description of procedures is provided in earlier publications (Mazarati et al., 2008, 2009a).

Forced swim test (FST)

FST allows examining state of despair and is based on the innate ability of rats to adopt active strategies in the inescapable stressful situation (Pucilowski and Overstreet, 1993). FST consisted of a single 5-min swimming session in the tank (height, 60 cm; diameter, 30 cm) filled with water at 22–25 °C. Swimming behavior was videotaped and analyzed offline. Cumulative immobility time (Fig. 2A) was calculated. The increased immobility time indicates the state of despair (Mazarati et al., 2008; Pucilowski and Overstreet, 1993).

Taste preference test

This test for anhedonia is based on the innate preference of rodents towards sweets (Pucilowski et al., 1993). Taste preference was examined using saccharin solution consumption test (Mazarati et al., 2008; Pucilowski et al., 1993). The rat's cage was supplied with two 250-ml graduated bottles, one filled with water and another filled with 0.1% saccharin solution. Taste preference was expressed as percent of the volume of saccharin solution of a total volume of fluid (saccharin plus water) consumed over 24 h. The loss of preference for saccharin (i.e. consumption of statistically equal volumes of saccharin and water) is indicative of anhedonia (Mazarati et al., 2008; Pucilowski et al., 1993).

Plasma corticosterone (CORT) assay

Measurement of baseline plasma CORT level and dexamethasone/corticotropin releasing hormone (DEX/CRH) test were performed upon the completion of behavioral tests (Johnson et al., 2006; Mazarati et al., 2009a; Pohorecky et al., 2004; Steimer et al., 2007). Between 8:00"" and 10:00 AM, 50–100 μl of blood was collected from the tail vein into the EDTA-coated tubes. The animals were then injected into the tail vein with DEX (Sigma; 0.03 mg/kg). Six hours later blood was collected again, and animals were injected into the tail vein with CRH (Sigma; 50 ng/kg); two blood samples were taken 30 and 60 min after CRH injection. CORT was detected in 10-μl plasma samples, using Immunochem™ Double Antibody Corticosterone 125I RIA kit (MP Biomedicals, Orangeburg, NY). Dysregulation of the HPA axis in depression consists of the elevated baseline CORT level; failure of DEX to suppress CORT; and exacerbated and prolonged increase of CORT in response to CRH (the latter two impairments constitute positive DEX/CRH test) (Johnson et al., 2006; Mazarati et al., 2008, 2009a; Pohorecky et al., 2004; Zobel et al., 2004).

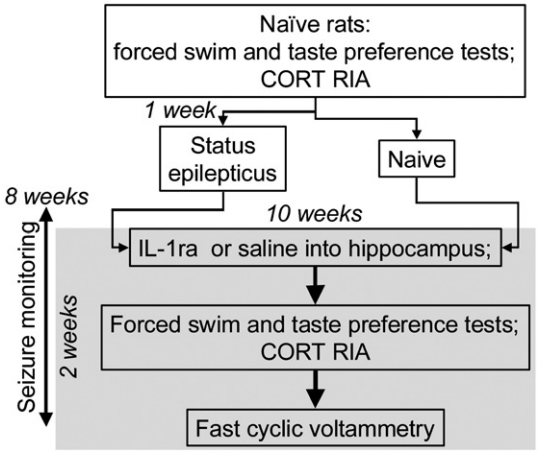

Fig. 1. Experimental design. Explanations are in the Methods section.

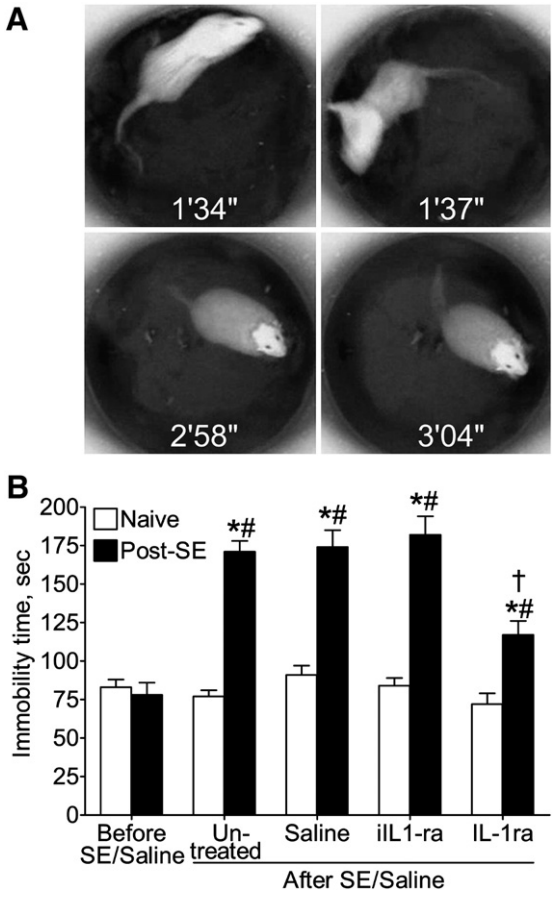

Fig. 2. Effects of IL-1ra treatment on the forced swimming behavior. (A) Sample snapshots taken from pre-recorded video during FST. Time after the start of the test is indicated on each image. Examples of active swimming which reflects active escape strategies are presented at 1 min 34 s and 1 min 37 s. Note the change in the rat's position in the tank, which occurred during the 3-s period, and the fuzziness of images due to the animal's movement. Examples of immobility when animals move only enough to avoid drowning are presented at 2 min 58 s and 3 min 04 s. Note that the animal's position in the tank did not change during 6 s of recording and that the body is positioned vertically in the water. (B) Immobility time in naive and post-SE animals—untreated, treated with saline, heat-inactivated IL-1ra (iIL-1ra) or active IL-1ra. Note the increase in the cumulative immobility time in untreated, saline-treated and iIL-1ra-treated post-SE animals and its partial reversal following IL-1ra administration. Data are presented as mean ± SEM. *$p<0.05$ after SE vs. before SE (repeated measure ANOVA + Newman–Keuls *post hoc* test); #$p<0.05$ post-SE vs. naive; †$p<0.05$ post-SE IL-1ra vs. post-SE saline (one-way ANOVA + Newman–Keuls *post hoc* test).

Status epilepticus (SE)

Two days after DEX/CRH test, animals received intraperitoneal injection of LiCl (130 mg/kg, Sigma, St. Louis, MO) and 24 h later—subcutaneous injection of pilocarpine (40 mg/kg, Sigma). Behavioral seizures were monitored during SE. SE was characterized by continuous limbic seizures starting 10–15 min after pilocarpine injection. Three and eight hours after seizure onset, rats were injected intraperitoneally with diazepam (5 mg/kg) and phenytoin (50 mg/kg) in order to alleviate further seizures and to decrease mortality. In control animals, pilocarpine was substituted with saline.

Monitoring of spontaneous seizures

Due to the complexity of the drug delivery system, monitoring of spontaneous seizures was limited to video. Beginning from 8 weeks after SE and until the end of experiments, animals' behavior was continuously recorded using digital camera. Seizures were analyzed offline. Two seizure types were considered: focal seizures (motor arrest, facial twitches and mastication) and generalized clonic or