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DEPRESSION- AND ANXIETY-LIKE BEHAVIORS OF A RAT MODEL WITH ABSENCE EPILEPTIC DISCHARGES

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Abstract—Depression and/or anxiety are major comorbidities of epilepsy. However, the contribution of absence epileptic discharges in psychiatric syndromes is inconclusive. This study aimed to clarify the influence of absence seizure in anxiety- and depression-like behaviors using normal Wistar rats and Long-Evans rats with spontaneous spike-wave discharges (SWDs). Anxiety-like behaviors were evaluated by the open field (OF) and elevated plus maze (EPM) tests, and depression-like behaviors by the forced swimming (FS) and sucrose consumption (SC) tests. Long-Evans rats displayed significantly higher frequency and longer duration in the open arms of the EPM and in the center zone of the OF than did Wistar rats. Normalized behavioral indexes by movement also were significantly higher in Long-Evans rats. An excess of SWD numbers was associated with lower indexes and worse movement in the two behavioral tests. Ethosuximide eliminated the seizure frequency-dependent relationship and also significantly increased all indexes of the EPM test. Additionally, Long-Evans rats revealed significantly longer immobility in the FS test and lower consumption of sucrose solution in the SC test than did Wistar rats. Meanwhile, no relationship was found between immobility of the FS test and SWD number. Ethosuximide ameliorated depression-like behavior of Long-Evans rats that was equal to that of Wistar rats. Thus, Long-Evans rats showed seizure frequency–related exacerbation in anxiety-like behavior; and they displayed a depressive propensity. Our data suggest that generalized SWDs may have distinct influences in anxious and depressive behaviors.

Key words: absence epilepsy, depression, anxiety, spike-wave discharge, ethosuximide.

Epilepsy is characterized by generalized or partial aberrant activity of the brain, and it often affects behavioral and cognitive functions. Frontal cortex is known to be related to several aspects of functions, such as motor programming and execution, emotional control, etc. Dysfunction in the frontal cortex can result in motor impairment or psychiatric disorders. For instance, anxiety and depression appear in a considerable proportion of patients with frontal lobe epilepsy (Shulman, 2000; Helmstaedter, 2001; Kanner, 2004) or a lesion of the frontal lobe (Starkstein et al., 1987; House et al., 1990; Mathew et al., 2004). Numerous epidemiological studies have indicated that depression and/or anxiety are major comorbidities of epilepsy (Caplan et al., 2005; Kanner and Balabanov, 2002; Plioplys, 2003), whether and how aberrant activity of the brain results in psychiatric disorders remains largely unknown. Several confounding factors, such as multiple types of epilepsy included in studies and patients taking various antiepileptic drugs, often lead to inconclusive and controversial results (Austin et al., 1992; Ettinger et al., 1998; Oguz et al., 2002; Baki et al., 2004; Adewuya and Ola, 2005). Likewise, antiepileptic drugs can ameliorate or aggravate psychiatric symptoms (Monaco and Cicolin, 1999; Schmitz, 1999). To elucidate the contribution of seizure activity in anxiety and depression, a single type of epilepsy and the situation without antiepileptic drugs are critical. Animal models have been discovered to be an indispensable approach to search the etiology and pathogenesis of neurological or psychiatric disorders (Danober et al., 1998; Crunelli and Leresche, 2002; Nestler et al., 2002). Therefore, animal models with spontaneous epileptic discharges may provide a chance to elucidate the relationship between seizure and psychiatric disorders.

Spontaneous spike-wave discharges (SWDs), which are prominent in frontoparietal cortical regions, appear in particular rat strains, such as WAG/Rij, GAERS, and Long-Evans rats (Kaplan, 1985; Danober et al., 1998; Crunelli and Leresche, 2002; Coenen and van Luijtelaar, 2003; Shaw, 2004). Numerous aspects of results in Long-Evans rats, including bilateral synchronous SWDs in coincidence with minor whisker twitching during sudden immobility, SWDs frequently occurring at the transition of vigilance states, unresponsiveness to mild stimuli during SWDs, similarity between spontaneous SWDs and proconvulsant-induced paroxysmal activities, significant reduction of SWD occurrence by anti-absence drugs (ethosuximide (ESM), valproic acid, and diazepam) with dose-dependent manners, etc., have indicated the association between SWDs and typical absence seizures (Shaw, 2004, 2007; Shaw and Liao, 2005; Shaw et al., 2006). The coexistence of anxiety and depression is observed in a portion of subjects with epilepsy (Oguz et al., 2002; Adewuya and

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Abbreviations: CZ, center zone; EPM, elevated plus maze; ESM, ethosuximide; FS, forced swimming; OA, open arm; OF, open field; SC, sucrose consumption; SWD, spike-wave discharge.

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Ola, 2005), but it is inconclusive in patients with absence epilepsy (Ettinger et al., 1998; Oguz et al., 2002; Baki et al., 2004; Caplan et al., 2005) and rats with spontaneous SWDs (Sarkisova et al., 2003; Jones et al., 2008). To clarify the contribution of SWDs in anxiety- and depression-like behaviors, we used Long-Evans rats with spontaneous absence epileptic discharges to ask if SWD was related to alteration of anxiety- and depression-like behaviors. The relationship between the seizure frequency and anxiety- and depression-like behaviors was examined. Moreover, ESM, a first choice anti-absence drug with little psychiatric side effect (Rao et al., 1991; Schmitz, 1999; Reijs et al., 2004), was used to understand the contribution of SWDs in psychiatric disorders.

EXPERIMENTAL PROCEDURES

Animal preparations and recordings

Adult male Long-Evans and Wistar rats were used. Wistar rats were selected as an experimental control because they have been commonly used in previous studies (Sarkisova et al., 2003; Jones et al., 2008). All rats were kept in a sound-attenuated room under a 12-h light/dark cycle (07:00–19:00 h lights on) with food and water provided *ad libitum*. The experimental procedures were reviewed and approved by the Institutional Animal Care and Use Committee. All experiments complied with NIH (USA) recommended guidelines on the ethical use of animals. Detailed experimental and recording procedures were described previously (Shaw et al., 2002). Briefly, the recording electrodes were implanted under pentobarbital anesthesia (60 mg/kg i.p.). Subsequently, the rat was placed in a standard stereotaxic apparatus. In total, six stainless steel screws were driven bilaterally into the skull overlying the frontal (anterior +2.0, lateral 2.0 with reference to the bregma), parietal (anterior –2.0, lateral 2.0), and occipital (anterior –6.0, lateral 2.0) regions of the cortex to record cortical field potentials. A ground electrode was implanted 2 mm caudal to lambda. Dental cement was applied to fasten the connection socket to the surface of the skull. Following suturing to complete the surgery, animals were given an antibiotic (chlortetracycline) and housed individually in cages for recovery.

Two weeks after surgery, animals were individually placed in clear acrylic chambers to record brain activities. To allow rats to habituate to the recording apparatus, each rat was placed in the acrylic chamber at least five times (1 h/day) prior to the recording. On the day of the recording, a 30-min period was allowed for the rat to become familiar with the chamber. Monopolar cortical activities recorded from skull electrodes were buffered with field-effect transistors and amplified (Shaw et al., 2002). SWDs were characterized by a barrage of large sharp spike discharges (>0.4 mV) with negative polarity which were prominent in the frontal and parietal regions (Fig. 1). SWDs suddenly occurred in coincidence with immobility. SWDs sometimes were accompanied by facial/whisker twitching. Whisker twitching behavior occurs at the beginning of a considerable portion of SWDs, particularly for rats with high-frequency occurrence of SWDs (Shaw and Liao, 2005). The power spectra of SWDs displayed a dominant frequency peak of around 7–12 Hz accompanied by several harmonics. These criteria have been well documented in previous studies (Shaw, 2004, 2007).

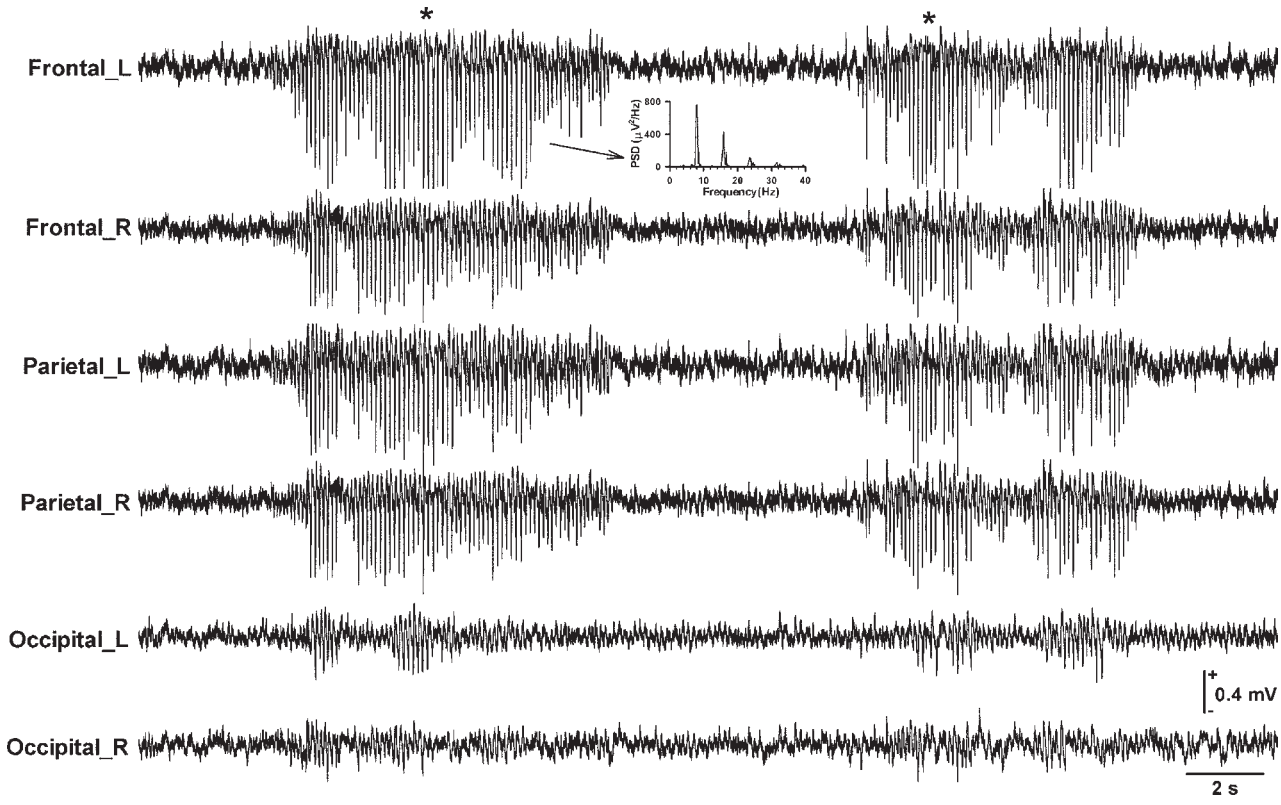

Fig. 1. A representative example of spontaneous SWDs. Paroxysmal SWDs (*) were prominent and bilaterally synchronous in the frontal and parietal cortices with a small extent in the occipital cortex. SWDs oscillated in the range of 7–12 Hz accompanied by several harmonics (inset). PSD, power spectral density.