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7-12 Hz High-Voltage Rhythmic Spike Discharges in Rats Evaluated by Antiepileptic Drugs and Flicker Stimulation

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Shaw F-Z. 7-12 Hz high-voltage rhythmic spike discharges in rats evaluated by antiepileptic drugs and flicker stimulation. *J Neurophysiol* 97: 238–247, 2007. First published October 11, 2006; doi:10.1152/jn.00340.2006. Paroxysmal 7- to 12-Hz high-voltage rhythmic spike (HVRS) or spike-wave discharges often appear in several particular strains of rats. However, functional hypotheses of these 7-12 Hz high-voltage cortical oscillations (absence seizure vs. idling mu rhythm) are inconclusive. The mu rhythm can be provoked by flicker stimulation (FS) in most people, but FS is less effective at eliciting absence epileptic activity. Therefore FS and antiepileptic drugs were used to verify the role of HVRS activity in Long-Evans rats with spontaneous HVRS discharges and Wistar rats without spontaneous HVRS discharges. The occurrence of HVRS discharges was significantly reduced by antiabsence drugs (ethosuximide, valproic acid, and diazepam) in dose-dependent manners, but high-dose carbamazepine displayed little effect. On the other hand, oscillation frequencies and durations of spontaneous HVRS discharges were not altered by FS. Under asynchronous brain activity, many FSs (>60%) elicited small-amplitude mu-rhythm-like activity in the barrel cortex concomitant with FS-related rhythms in the occipital cortex and resulted in significant augmentation of 7-12 Hz power in the parietal region. Furthermore, a large portion of FSs (>60%) revealed increase of 7-12 Hz power of the parietal cortex after ethosuximide administration (100 mg/kg ip) in Long-Evans rats. Similar FS-elicited phenomena also appeared in Wistar rats. Characteristics of FS-elicited mu-rhythm-like activities were consistent with those observed in humans, and they remarkably differed from those of spontaneous HVRS discharges. These results support the hypothesis that HVRS activity in Long-Evans rats may be an absence-like seizure activity rather than the mu rhythm.

INTRODUCTION

Several particular strains of rats, e.g., Long-Evans, Brown Norway, WAG/Rij, and GAERS, often display spontaneous 7-12 Hz high-voltage cortical oscillations (Buzsaki et al. 1990; Crunelli and Leresche 2002; Kaplan 1985; Willoughby and Mackenzie 1992). In general, 7-12 Hz high-voltage cortical oscillations in WAG/Rij and GAERS rats, called spike-wave discharges (SWDs), are believed to be associated with absence epilepsy (Coenen et al. 1991; Crunelli and Leresche 2002; Danober et al. 1998). However, the role of 7-12 Hz brain oscillations in Long-Evans rats, named high-voltage rhythmic spike (HVRS) discharges here, is the subject of debate: absence seizure (Kaplan 1985; Polack and Charpier 2006; Shaw 2004) or mu rhythm (Fontanini and Katz 2005; Nicolelis et al. 1995; Sakata et al. 2005; Semba et al. 1980). Numerous aspects of characteristics of HVRS discharges and SWDs are quite similar to each other. For instance, spontaneous bilaterally synchronous HVRSs/SWDs, which preferentially occur at the transition between wakefulness and sleep, abruptly appear during animal immobility sometimes in coincidence with whisker tremors (Coenen et al. 1991; Danober et al. 1998; Nicolelis et al. 1995; Shaw 2004; Shaw and Liao 2005). Cellular operations in the thalamocortical (Nicolelis et al. 1995; Pinault 2003; Polack and Charpier 2006) and corticostriatal (Berke et al. 2004; Magill et al. 2005; Slaght et al. 2004) networks during HVRSs/SWDs display comparable patterns. Moreover, the perioral/whisker representative region of the primary somatosensory cortex (SI) is very crucial for the generation of spontaneous HVRSs/SWDs (Fanselow et al. 2001; Gurbanova et al. 2006; Manning et al. 2004; Meeren et al. 2002; Sitnikova and van Luijtelaar 2004). Spontaneous HVRSs/SWDs can be successfully suppressed by ethosuximide (ESM) (Marescaux et al. 1984; Peeters et al. 1988; Shaw 2004), a first-choice antiabsence drug (Niedermeyer 1999b; Rogawski and Porter 1990). Although electrophysiological and pharmacological results support the association of HVRS activities and SWDs with absence seizures, the characteristics described in the preceding text could not absolutely rule out the possibility of a relationship between HVRSs/SWDs and the mu rhythm. Thus the role of spontaneous 7-12 Hz HVRSs/SWDs should be clarified before advanced application of these rats as absence epileptic animal models.

In humans, the mu rhythm is characterized by a small-amplitude sharply negative and a rounded positive phase in most instances (Niedermeyer 1999a), and its frequency falls in the alpha frequency range (8–13 Hz). The display of the mu rhythm is restricted to the rolandic region (Hari and Salmelin 1997; Niedermeyer 1999a), and the mu rhythm is functionally associated with idling somatosensory activity (Hughes and Crunelli 2005; Pfurtscheller et al. 1996). Although spontaneous mu rhythms only exist in a small proportion of the human population (Niedermeyer 1999a), mu rhythms can be provoked by various types of visual stimulation in most cases (Brechet and Lecasble 1965; Niedermeyer 1999a; Pfurtscheller 2003). In contrast, flicker stimulation (FS) is less effective in or only case dependent for eliciting absence epileptic discharges (Covanis et al. 1992; Mirsky et al. 1986; Niedermeyer 1999b; Takahashi and Fujiwara 2004). Accordingly, FS may help differentiate the association of 7-12 Hz HVRS discharges with the mu rhythm or absence seizures.

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Antiepileptic drugs are typically used to verify experimental epileptic animal models (Snead et al. 1999). In humans, ESM, valproic acid (VPA), and diazepam (DZP) successfully suppress the occurrence of SWDs, but carbamazepine (CBZ) has little effect on or increase the occurrence of spontaneous SWDs (Niedermeyer 1999b; Rogawski and Porter 1990). The effects of all these drugs on spontaneous 7-12 Hz SWDs in WAG/Rij and GAERS rats have been evaluated, and the results agree with those observed in absence epileptic patients (Marescaux et al. 1984; Peeters et al. 1988). However, the effects of these antiepileptic drugs on spontaneous HVRS activities have not been systematically assessed in Long-Evans rats (Shaw 2004). In this study, I attempted to answer the following questions: does FS provoke the mu rhythm and enhance 7-12 Hz power in the parietal region? Is the mu activity elicited by FS similar to spontaneous HVRS discharges or not? Are the effects of antiepileptic drugs on spontaneous HVRS discharges similar to those observed in patients with absence epilepsy?

METHODS

Adult Long-Evans ($n = 24$, 6–9 mo old) and Wistar ($n = 5$, 6–8 mo old) rats were used. The experimental procedures were reviewed and approved by the Institutional Animal Care and Use Committee. Detailed experimental and recording procedures were described previously (Shaw et al. 2002). Briefly, the recording electrodes were implanted under pentobarbital anesthesia (60 mg/kg ip). Subsequently, the rat was placed in a standard stereotaxic apparatus. The dorsal surface of the skull was exposed and cleaned. Six stainless steel screws were driven bilaterally into the skull overlying the frontal (A +2.0, L 2.0 with reference to the bregma), parietal (A −2.0, L 5.0), and occipital (A −6.0, L 2.0) regions of the cortex to record cortical field potentials (FPs). A ground electrode was implanted 2 mm caudal to lambda. The parietal lead was placed over the whisker and perioral representative area of the SI (Shaw and Liao 2005). In addition, two seven-strand stainless steel microwires (No. 7935, A-M Systems) were bilaterally inserted into the dorsal neck muscles to record electromyograms (EMGs). Dental cement was applied to fasten the connection socket to the surface of the skull. After suturing to complete the surgery, animals were given antibiotic (chlortetracycline) and housed individually in cages for recovery.

Two weeks after surgery, animals were individually placed in clear acrylic chambers so that their behaviors could easily be monitored. To allow rats to habituate to the experimental apparatus, each rat was placed in the recording environment ≥5 times (1 h/d) prior to testing. On the day of the recording, a 30-min period was allowed for the rat to become familiar with the chamber. All recordings were performed from 10:00 to 16:00 to minimize circadian variations. After completion of the experiment, the animal was killed with an overdose of pentobarbital sodium (120 mg/kg ip).

Monopolar FPs (0.3–1,000 Hz) recorded from skull electrodes, and the bipolar EMGs of neck muscles (100–500 Hz) were buffered with field-effect transistors and amplified (Shaw et al. 2002). A grounded plate was placed under the recording chamber to reduce electromagnetic interference (Shaw et al. 2003). All electrical signals were digitized at 2 kHz with a 12-bit A/D card (PCI6023E, National Instruments, Austin, TX). HVRS activities were characterized by a barrage of large sharp spike discharges (>0.4 mV) with negative polarity (Fig. 1). HVRS discharges were prominent in the frontal and parietal leads. In addition, the power spectra of HVRS activities displayed a dominant frequency peak of around 7–12 Hz accompanied by several harmonics. These criteria have been well documented in previous studies (Meeren et al. 2002; Shaw 2004). To further characterize the spectrotemporal property, time-frequency analysis was carried out by consecutive 2-s Fourier transformations with a Hamming window and the data segments were selected with 50% overlapping.

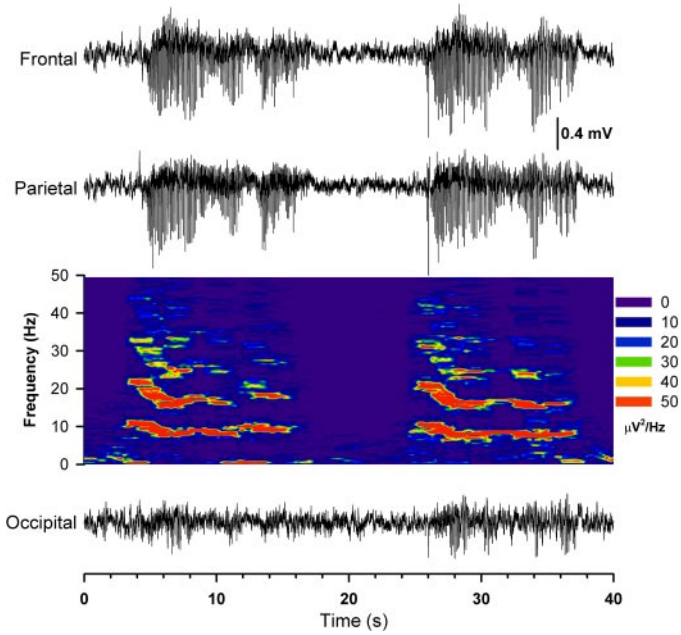

FIG. 1. A representative example of spontaneous high-voltage rhythmic spike (HVRS) discharges. The time-frequency data were calculated from the parietal field potential (FP). Paroxysmal HVRS activities were prominent in the frontal and parietal cortices with a small extent in the occipital cortex. HVRS discharges oscillated in the range of 7–12 Hz accompanied by several harmonics. The oscillation frequency at the beginning of HVRS discharges was higher than those of the remaining segments of HVRS discharges.

The effects of four antiepileptics (antiabsence: ESM, VPA, and DZP; anticonvulsant: CBZ) on human absence epilepsy are well known. ESM, DZP, and VPA (Sigma) were diluted in normal saline. CBZ (Sigma) was dissolved in a mixture of 50% distilled water, 10% ethanol, and 40% propylene-glycol. The doses of antiepileptics in common clinical use were used (Hardman and Limbird 2001), i.e., ESM (>12.5 mg/kg), DZP (>0.5 mg/kg), VPA (>25 mg/kg), and CBZ (>5 mg/kg). Drugs were randomly injected in a volume of 2 ml/kg (ip) to evaluate their effects on spontaneous HVRS discharges in Long-Evans rats ($n = 10$). Doses and drugs were applied in a random order by the computer-generated random number. A minimum of 7 days elapsed between any two injections. Animals were acclimated to the apparatus for 30 min, then a 60-min FP was recorded as the baseline. The total HVRS duration in the 60-min period starting 20 min after the injection was compared with the total HVRS duration of a 60-min period before the injection which was taken as 100%.

FSs with seven flicker rates (Flash 10, Micromed, Italy) were utilized for evaluating changes in brain activities of Long-Evans rats ($n = 8$). FSs were performed under a quiescent state but not in the waking moving state. The intensity of the FSs for five seconds was set at grade 9 (range, 1–10), and the distance between the FS and rat was 15–20 cm. To characterize the effect of FS, two distinct brain states, i.e., asynchronous brain activity and paroxysmal HVRS discharges, were evaluated. Under spontaneous HVRS discharges, at least a 5-s pause was interposed between two consecutive FSs. The durations and oscillation frequencies of HVRS discharges during FS were compared with those in the absence of FS. Termination of spontaneous HVRS discharges by FS, which was defined by ≥5 s of normal brain activity after FS, was also measured. During asynchronous brain activity, interstimulus intervals of the FSs exceeded 5 s to reduce adaptation of the animal to the FS. The power spectra of the FPs were obtained by Fourier transformation with a Hamming window. Powers of FPs in the range of 7–12 Hz before and during FS were compared. At least 50 FSs were carried out in each flicker rate.

In third part of the experiment, effects of ESM (100 mg/kg ip) on FS-evoked cortical responses were compared in both Long-Evans rats

($n = 6$) and Wistar rats ($n = 5$). FSs of 15 Hz for 5 s were used in the experiment. Interstimulus intervals of the FSs exceeded 5 s. In these Wistar rats, no spontaneous HVRS discharges were found in 6-h recordings (10:00–16:00) for 3 days and during FS experiment (see RESULTS). All FSs were performed under a quiescent state. In the ESM group, FS experiment started 30 min after ESM injection.

Data are expressed as the means ± SE in the present study. One-way repeated measures ANOVA (on ranks) was used to evaluate the dose-responses of antiepileptic drugs on spontaneous HVRS discharges as well as the effect of different flicker rates of FSs in changes of the parietal cortical activities under spontaneous HVRS discharges and asynchronous brain activity. Multiple comparison analyses between groups were carried out by paired *t*-test.

RESULTS

Effect of antiepileptic drugs on spontaneous HVRS discharges

Figure 1 depicts a representative example of spontaneous HVRS discharges. HVRS activity prominently appeared in the frontal and parietal cortices with a small extent in the occipital cortex. HVRS discharges revealed a dominant oscillation frequency of 7–12 Hz accompanied by several harmonics. Oscillation frequencies of HVRS discharges were higher at the beginning. Mean durations of spontaneous HVRS discharges ($n = 10$) were 10.66 ± 0.87 (range, 1.15–112.4) s. Although the number and duration of HVRSs varied individually, the number ($P = 0.51$ by 1-way repeated-measures ANOVA) and total duration ($P = 0.92$) of HVRS activities 1 h before drug administration were stable throughout the 12-wk recording period (Fig. 2*A*). Subsequently, the effects of antiepileptic drugs on spontaneous HVRS discharges were evaluated. Representative examples of spontaneous activities of the parietal cortex with or without antiepileptic drugs are shown in the upper panel of Fig. 2*B*. No obvious change in the configuration of spontaneous HVRS discharges was observed during the administration of antiepileptic drugs. Total HVRS durations were significantly reduced by ESM ($P < 0.0005$), VPA ($P <$

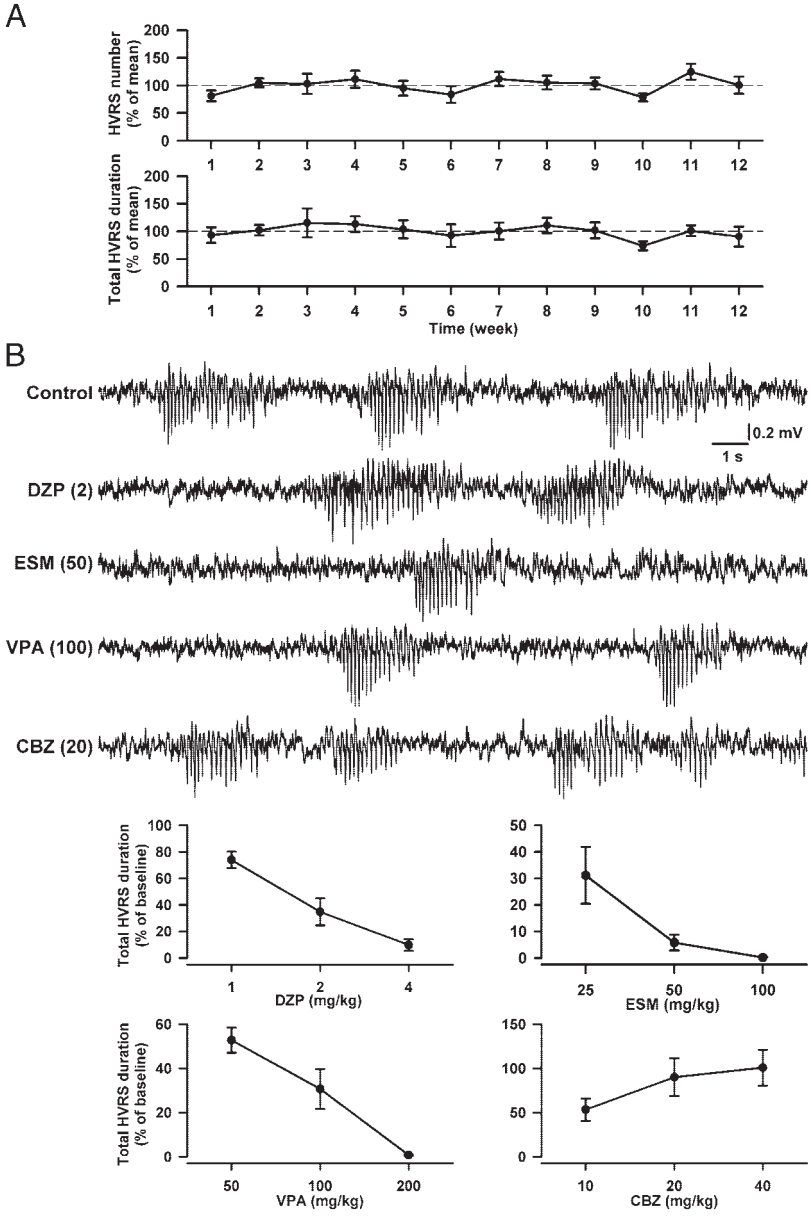

FIG. 2. Effect of antiepileptic drugs on spontaneous HVRS discharges ($n = 10$). *A*: fluctuations in the number and total duration of spontaneous HVRS discharges during the 12-wk recording period. The number and total duration of spontaneous HVRS discharges were calculated from the 1-h baseline recording prior to administration of antiepileptic drugs. Both the number and total duration of spontaneous HVRS discharges were stable throughout the recording period. *B*: effect of 4 antiepileptic drugs on spontaneous HVRS durations. *Top*: representative examples of spontaneous activities of the parietal cortex in the absence of drugs (control) and with antiepileptic drugs {2 mk/kg diazepam [DZP (2)], 50 mg/kg ethosuximide [ESM (50)], 100 mg/kg valproic acid [VPA (100)], and 20 mg/kg carbamazepine [CBZ (20)]} in a Long-Evans rats are shown. No remarkable change in the configuration of HVRS activities was found. The HVRS duration was significantly reduced by DZP, VPA, and ESM in dose-dependent manners. The HVRS duration was not reduced by a high dose of CBZ.

0.0001), and DZP ($P < 0.0001$) in dose-dependent manners (Fig. 2*B*). In contrast, HVRS duration was decreased at a dose of 10 mg/kg of CBZ but displayed little effect at the higher doses of CBZ ($P = 0.065$). Similar dose-response trends by four antiepileptic drugs were also found in the number of HVRS discharges (ESM: 25 mg, 30.0 ± 7.6%; 50 mg, 10.9 ± 6.5%; 100 mg, 0.8 ± 0.8%; $P < 0.005$; VPA: 50 mg, 76.5 ± 17.9%; 100 mg, 57.0 ± 15.8%; 200 mg, 3.0 ± 1.8%; $P < 0.005$; DZP: 1 mg, 90.9 ± 19.4%; 2 mg, 43.7 ± 9.9%; 4 mg, 17.0 ± 8.1%; $P < 0.005$; CBZ: 10 mg, 61.6 ± 9.4%; 20 mg, 97.8 ± 27.1%; 40 mg, 98.6 ± 20.4%; $P = 0.32$).

Effect of FS during spontaneous HVRS discharges and normal ongoing EEG

Figure 3*A* depicts a representative example of brain activity under FS by time-frequency analysis. Temporal and spectral characteristics of HVRS discharges under FS (Fig. 3*A*) displayed no remarkable difference compared with those without FS (Fig. 1). Magnitudes of the HVRS discharges were not altered (no FS, 191 ± 15; 1 Hz, 194 ± 15; 5 Hz, 194 ± 16; 10 Hz, 190 ± 14; 15 Hz, 187 ± 13; 20 Hz, 194 ± 17; 25 Hz, 190 ± 17; 30 Hz, 190 ± 17 μV rms; $P = 0.81$ by 1-way repeated-measures ANOVA, $n = 8$). Oscillation frequencies of the HVRS discharges did not change significantly (no FS, 8.30 ± 0.17; 1 Hz, 8.29 ± 0.16; 5 Hz, 8.29 ± 0.23; 10 Hz, 8.13 ± 0.21; 15 Hz, 8.34 ± 0.19; 20 Hz, 8.29 ± 0.17; 25 Hz, 8.34 ± 0.16; 30 Hz, 8.41 ± 0.11 Hz; $P = 0.24$). Durations of the HVRS discharges displayed remarkable change neither (no FS, 5.49 ± 1.26; 1 Hz, 5.14 ± 0.94; 5 Hz, 5.48 ± 1.26; 10 Hz, 5.11 ± 0.19; 15 Hz, 5.55 ± 1.33; 20 Hz, 5.86 ± 1.52; 25 Hz, 5.54 ± 1.31; 30 Hz, 5.75 ± 1.43 s; $P = 0.31$). Moreover, only a small proportion of the FS (<20%) was able to block spontaneous HVRS discharges (Fig. 3*B*). Termination of HVRS discharges was not dependent on flicker rates ($P = 0.71$).

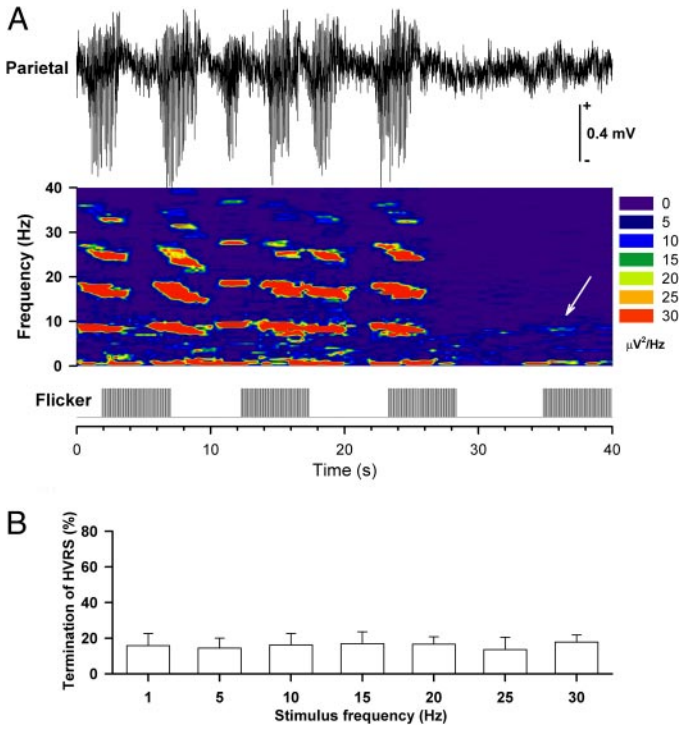

FIG. 3. Cortical responses to flicker stimulation (FS) under spontaneous HVRS discharges ($n = 8$). *A*: representative example of the time-frequency activity of the parietal cortex in response to a series of 15-Hz FSs. FS had no effect on the oscillation frequency of HVRS discharges. Under normal background brain activity, FS elicited an increase in ~10-Hz power at the beginning of the FS (arrow). *B*: if the termination of a HVRS activity took place during FS and lasted >10 s, the FS was considered to be an effective stimulus to stop an HVRS discharge. Only a small proportion (<20%) of FSs were able to block HVRS activities.

Under asynchronous brain activity ($n = 8$), an obvious power enhancement in the alpha frequency range was seen during FS (Fig. 3*A*, arrow). No phasic motor activity was observed during FS. In the cases of increased alpha powers during FS, a small-amplitude sharply negative peak followed by a positive wave, which is analogous to the human wicket-shaped mu rhythms (Niedermeyer 1999a), was often observed during FS (Fig. 4). The evoked mu-rhythm-like activity was prominent in the parietal lead, and the FS-related rhythm displayed in the occipital cortex (Fig. 4). Obvious 7-12 Hz activity was seen in the filtered trace and power spectrum during FS. The evoked mu-rhythm-like activity usually revealed a dominant oscillation frequency in the alpha range and contained fewer harmonics. In another example, FS elicited mu-rhythm-like activity followed by HVRS activity (Fig. 4*B*). Obviously, the magnitudes of the evoked mu-rhythm-like activity and HVRS activity were different.

A large proportion (63.4–77.3%) of FSs with seven flash rates resulted in enhancement of the 7-12 Hz power, and only a small percentage (2.8–5.8%) of FSs elicited the complex of the mu-rhythm-like activity and HVRS discharge (Fig. 5*A*). The proportion of enhanced 7-12 Hz power was not related to the flicker rate ($P = 0.14$ by 1-way repeated-measures ANOVA). On average, the 7-12 Hz power was obviously enhanced during FS (Fig. 5*B*). When all traces were included in the analysis, great variance in 7-12 Hz power enhancement was observed. Because the powers of HVRS discharges during FS were extremely high compared with those of the evoked mu-rhythm-like activity, thus these HVRS activities might greatly contribute to the enhancement of 7-12 Hz powers. However, trials of FS-elicited HVRS activities varied individually. Therefore great variance in 7-12 Hz power enhancement was seen in the analysis of all traces. Considering trials without HVRS discharges, average 7-12 Hz powers were significantly augmented by FS in all flicker rates (Fig. 5*B*). Enhancement of 7-12 Hz power during FS was not significantly different in groups of flicker (all) and flicker (all-HVRS) except for 15 Hz FS. The augmenting effect was independent of flicker rate ($P = 0.32$).

Effect of ESM on FS-evoked mu-rhythm-like activity in Long-Evans and Wistar rats

Figure 6*A* depicts the change of brain activity by a 15-Hz FS before ESM injection in a Long-Evans rat. An obvious peak in the alpha frequency range was found in the parietal region during FS, and the FS-related rhythm revealed in the occipital lead. Similar phenomena were observed after ESM injection (Fig. 6*B*). In Long-Evans rats ($n = 6$), a small percentage of FSs (3.43 ± 1.82%) elicited HVRS discharges without ESM administration, but no HVRS activity was seen during FS after ESM injection. Moreover, a large proportion of FSs enhanced 7-12 Hz powers of the parietal lead before and after ESM injection (before, 71.7 ± 3.6%; after, 65.1 ± 2.6%, $P = 0.24$ by paired *t*-test) (Fig. 6*C*). On average, 7-12 Hz powers of the

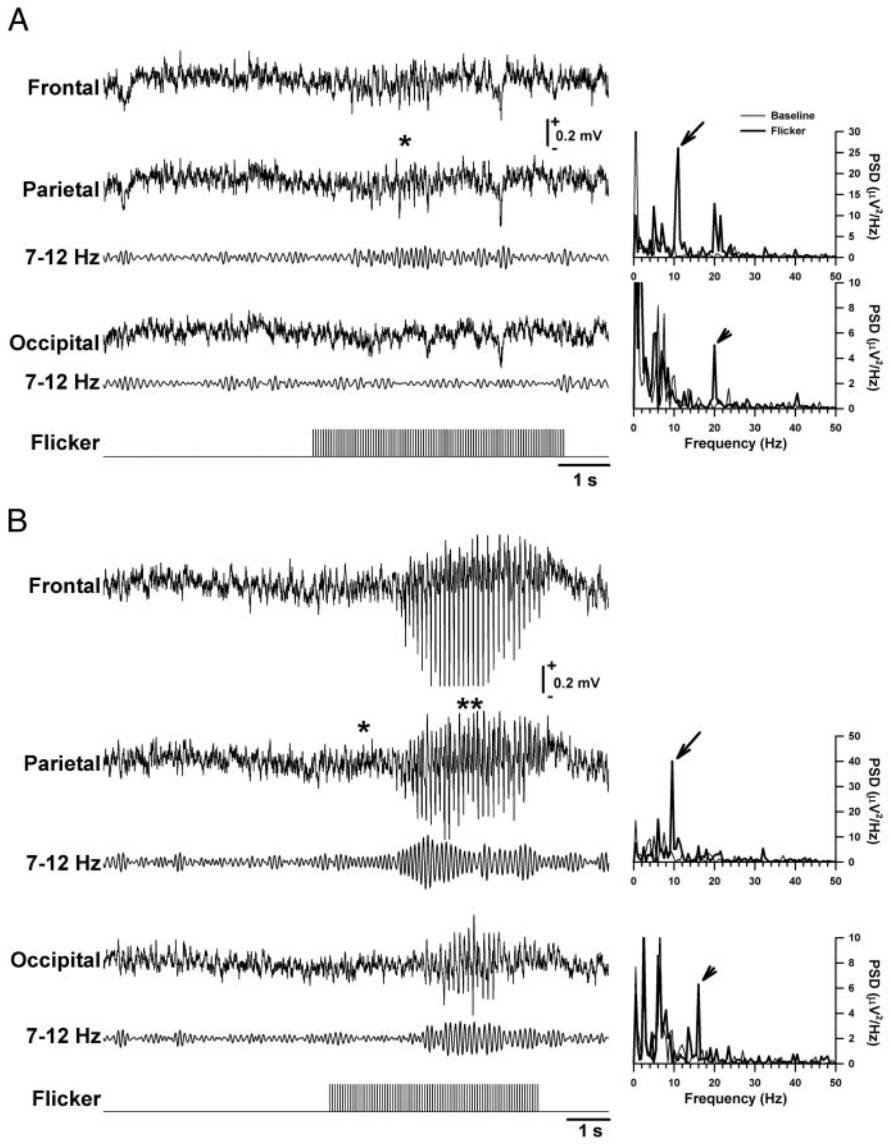

FIG. 4. Two representative examples of changes in the cortical activity by FS under asynchronous brain activities. *A*: small-amplitude sharply negative peak followed by a positive wave (asterisk) was recorded at the frontal and parietal leads during a 20-Hz FS. Obvious 7-12 Hz activity of the parietal FP derived from a zero-phase band-pass filter was shown in the filtered trace during FS. The enhancement of 7-12 Hz activity was not observed in the filtered trace of the occipital FP. The power distribution of particular frequencies differed before (thin line) and after (thick line) the FS. A prominent ~10 Hz peak (arrow) appeared in the parietal power spectrum. By contrast, a clear 20-Hz peak (arrowhead) appeared in the power spectrum of the occipital lead. PSD, power spectral density. *B*: during a 15-Hz FS, small-amplitude mu-rhythm-like activity (asterisk) was observed in the frontal and parietal leads and followed by a widespread HVRS discharge (double asterisk). During the period of FS-evoked mu-rhythm-like activity, the filtered trace of the occipital lead displayed no obvious increase of 7-12 Hz magnitude. In a sharp contrast, during HVRS discharges 7-12 Hz activity of the occipital lead concomitant with those of the frontal and parietal leads were enhanced. To reduce the influence of large-magnitude HVRS discharges on the FS-evoked responses, 2-s FP was selected to calculate the power spectrum. At the initial phase of FS, a clear peak (arrow) was shown in the 7-12 Hz range of the parietal power spectrum, and a 15-Hz peak (arrowhead) was displayed in the occipital power spectrum.

parietal lead were significantly increased during FS with and without ESM injection (Fig. 6*D*). The increased 7-12 Hz powers during FS were not significantly reduced by ESM (before, 187.0 ± 26.7%; after, 132.7 ± 4.5%, $P = 0.08$). In Wistar rats without spontaneous HVRS discharges ($n = 5$), no HVRS discharge was elicited by FS before and after ESM injection (Fig. 6*C*). A large proportion of FSs enhanced 7-12 Hz powers of the parietal lead before and after ESM administration (before, 77.0 ± 3.1%; after, 69.6 ± 0.8%, $P = 0.12$). 7-12 Hz powers of the parietal cortex were significantly increased by FS with and without ESM administration (Fig. 6*D*). The increased 7-12 Hz powers during FS were significantly reduced after ESM injection (before, 179.1 ± 5.9%; after, 150.3 ± 4.4%, $P = 0.013$). Comparison of several aspects of the characteristics of HVRS discharges and FS-evoked mu-rhythm-like activities is summarized in Table 1.

DISCUSSION

The major findings of this study were the number and total duration of spontaneous HVRS discharges were significantly reduced by antiabsence drugs (ESM, VPA, and DZP) in dose-dependent manners but revealed little effect by high-dose CBZ (40 mg/kg); under spontaneous HVRS discharges, FS did not alter oscillation frequencies or durations of HVRS discharges or terminate most HVRS activities; under asynchronous brain activity, most FSs (>60%) elicited small-amplitude mu-rhythm-like activities and produced a significant increase of the alpha power in the parietal area but not in the occipital region. Spatiotemporal characteristics of the evoked small-magnitude mu-rhythm-like activities strikingly differed from those of spontaneous high-amplitude HVRS discharges; and the occurrence of spontaneous HVRS discharges were significantly reduced by ESM but no remarkable effect was found in the occurrence of FS-evoked mu-rhythm-like activity (>60%) by ESM. Increased alpha power during FS was reduced by ESM. Similar FS-elicited phenomena were found in both Long-Evans and Wistar rats. This is the first study to clarify the relationship of the mu rhythm to HVRS discharges in rats.

Functional hypothesis of 7-12 Hz HVRS discharges in rats (absence seizure vs. mu rhythm) is being still debated (Fonta-

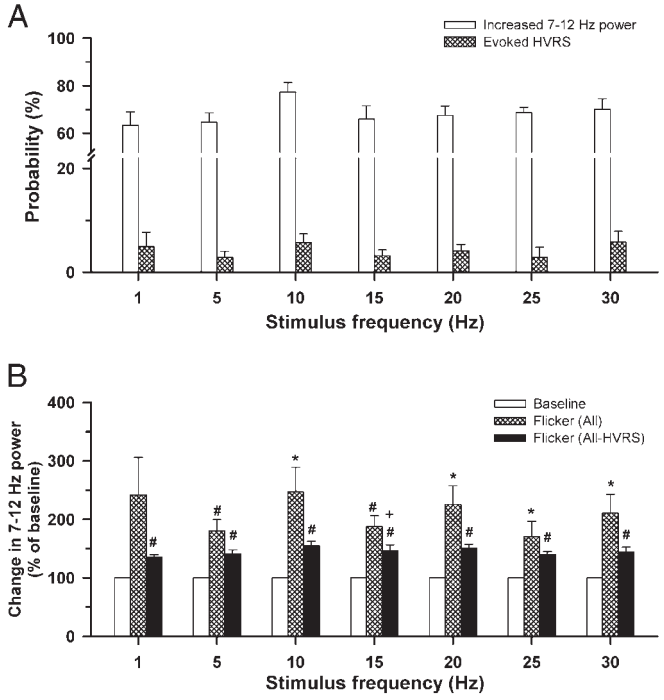

FIG. 5. Effects of FS on the activity of the parietal cortex under asynchronous brain activities ($n = 8$). *A*: large proportion (>60%) of FSs elicited enhancement of 7-12 Hz power during FS with 7 flicker frequencies. Rarely, FSs (<6%) provoked the complex of the mu-rhythm-like activity and HVRS discharge. *B*: powers at 7–12 Hz were increased by FS compared with those of the baseline. Because the 7-12 Hz power of an HVRS discharge was extremely high and the proportion of FS-elicited HVRS activities varied individually, great variance appeared in the results [flicker (all)]. Considering trials without HVRS discharges [flicker (all-HVRS)], 7-12 Hz power was significantly augmented by FSs for all flicker frequencies. Enhancement of 7-12 Hz power during FS was not significantly different in groups of flicker (all) and flicker (all-HVRS) except for 15 Hz FS. #, $P < 0.005$; *, $P < 0.05$ vs. the baseline by paired *t*-test. +, $P < 0.05$ vs. Flicker (all) by paired *t*-test.

nini and Katz 2005; Kaplan 1985; Nicolelis et al. 1995; Polack and Charpier 2006; Sakata et al. 2005; Semba et al. 1980; Shaw 2004). In the present study, I found that FS provoked mu-rhythm-like cortical activity and enhanced 7-12 Hz power at the parietal lead. These results are similar to observations in humans (Hari and Salmelin 1997; Niedermeyer 1999a; Pfurtscheller 2003). During FS, the occipital cortex displayed FS-related rhythmic activity. This is consistent with previous reports (Rager and Singer 1998; Wells et al. 2001). According to the dissociation of two different activities in parietal and occipital cortices during FSs, the evoked mu-rhythm-like activity appeared at the parietal lead was a local brain activity. In addition, a large proportion of FSs elicited mu-rhythm-like activity in both Long-Evans rats with spontaneous HVRS discharges and Wistar rats without spontaneous HVRS discharges. Only a few cases of FSs elicited HVRS discharges in Long-Evans rats but not in Wistar rats. These data may support the small-magnitude FS-elicited enhanced 7-12 Hz activity being similar to visual evoked mu rhythms in humans (Niedermeyer 1999a; Pfurtscheller 2003; Pfurtscheller et al. 1996). Furthermore, several aspects of properties of FS-evoked mu-rhythm-like activities in the temporal, spectral and spatial domains as well as the occurrence in response to ESM (100 mg/kg ip) strikingly differed from those of spontaneous HVRS discharges (Table 1). Moreover, no obvious motor activity appears in the occurrence of mu rhythms (Hari and Salmelin 1997; Niedermeyer 1999a; Pfurtscheller 2003), but whisker twitching is coincident with HVRS discharges (Nicolelis et al. 1995; Semba et al. 1980; Shaw and Liao 2005). These data may not support the hypothesis that 7-12 Hz HVRS discharges are the mu rhythm. Remarkably, HVRS discharges were significantly reduced by antiabsence drugs but displayed little effect with high-dose CBZ. The results of antiepileptic drugs are similar to those in absence epileptic patients (Niedermeyer 1999b; Rogawski and Porter 1990). Several additional lines of evidence concerning 7-12 Hz HVRS activity in rats, including bilateral cortical synchronization, appearance under immobility, higher oscillation frequency at the beginning, frequent occurrence at the transition between wakefulness and sleep, unresponsiveness to mild stimuli, coherent oscillations in the corticothalamic networks, and similarity between spontaneous HVRS discharges and proconvulsant-induced activities, are also similar to observations in absence epileptic patients (Crunelli and Leresche 2002; Nicolelis et al. 1995; Niedermeyer 1999b; Polack and Charpier 2006; Semba et al. 1980; Shaw 2004; Snead et al. 1999). Based on these results, 7-12 Hz HVRS discharges in rats may be associated with the hypothesis of absence seizures rather than the mu rhythm. Interestingly, enhanced 7-12 Hz powers during FS were reduced by intraperitoneal ESM administration, and spontaneous HVRS discharges were almost completely abolished by ESM at the same dose. These results may imply both FS-elicited mu-rhythm-like activity and spontaneous 7-12 Hz HVRS discharges sharing similar mechanism for their generations.

In the present study, a small portion of FSs (2–6%) could elicit the complex of mu-rhythm-like activity and HVRS discharges in Long-Evans rats but not in Wistar rats. The occurrence of HVRS discharges during FS may be due to random appearance in quiescent immobile animals because a large portion of FSs only elicited mu-rhythm-like activity in Long-Evans and Wistar rats and FS did not alter several HVRS properties. In addition, no HVRS activity was elicited by FS in Wistar rats. The other possibility for the genesis of FS-elicited HVRS discharges may be associated with the development from FS-elicited mu-rhythm-like activity. The pronounced existence of spontaneous mu rhythm may be associated with epileptic or other pathological conditions (Hughes and Crunelli 2005; Niedermeyer 1999a). Recently, a study (Pinault et al. 2006) indicates a waking 5-9 Hz corticothalamic oscillation being a pro-epileptogenic activity although oscillation frequencies at the beginning of HVRS discharges often are >9 Hz in the waking state (Fig. 1) (Sakata et al. 2005; Shaw 2004). However, why only a small portion of FS-related mu-rhythm-like activity could elicit HVRS discharges under a quiescent state remains to be solved.

The appearance of absence seizure in humans is often linked to impairment of consciousness because of sudden interruption of ongoing activity and rare responsiveness to gentle stimulation (Mirsky et al. 1986; Niedermeyer 1999b). However, the concept is slightly improved because humans with absence epilepsy are not completely unresponsive to external stimulation in particular behavioral paradigms (for a review, see Blumenfeld 2005). In rats, most episodes of HVRS discharges (>80%) are continuously displayed during mild whisker/tail somatic stimulations (Nicolelis et al. 1995; Semba et al. 1980; Shaw 2004; Shaw et al. 2006) or visual stimulation (Inoue et al.

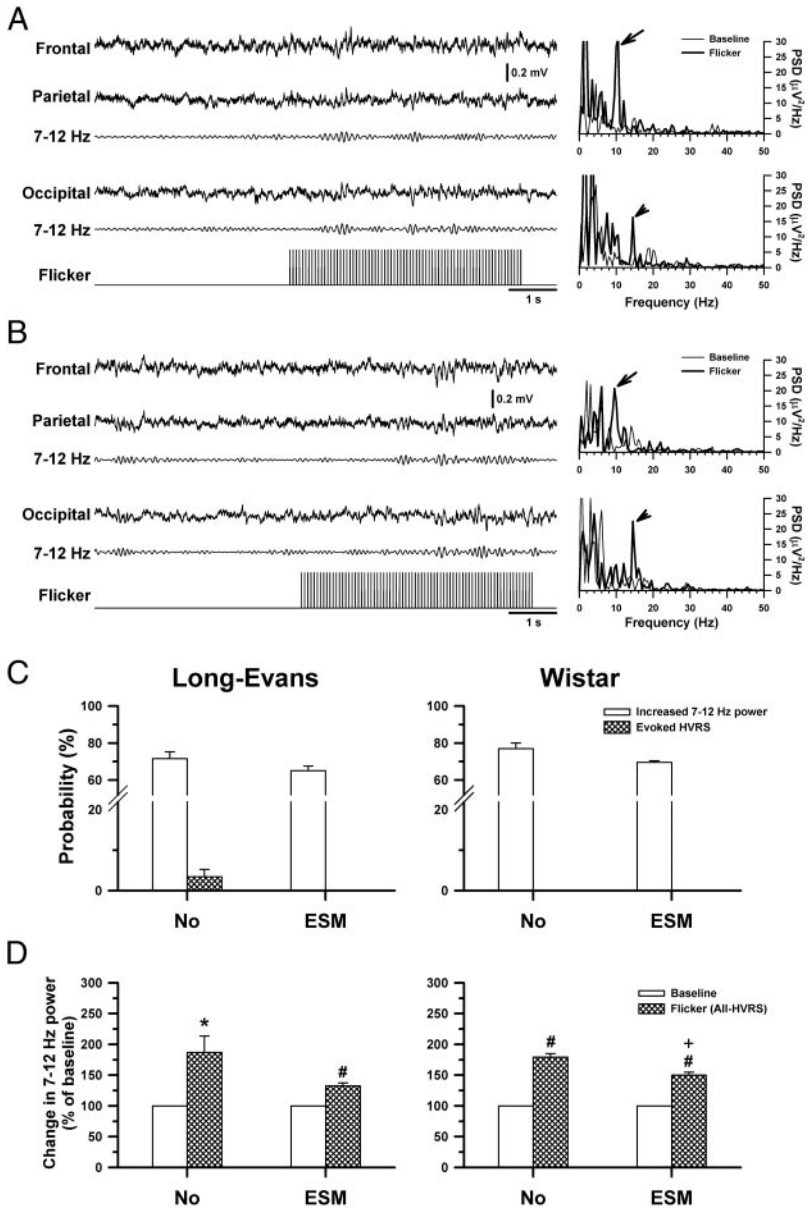

FIG. 6. Cortical responses during 15-Hz FSs before and after ESM administration in Long-Evans rats with spontaneous HVRS discharges ($n = 6$) and Wistar rats without spontaneous HVRS discharges ($n = 5$). Similar changes in the cortical activity by FS before (*A*) and after (*B*) ESM injection were observed in a Long-Evans rat. During FS, a prominent ~10 Hz peak (arrow) and a clear 15-Hz peak (arrowhead) appeared in the power spectra of the parietal and occipital leads, respectively. The FS-elicited responses were similar before and after ESM administration. *C*: comparison of the proportion of increased 7-12 Hz powers by FS before and after ESM injection in Long-Evans and Wistar rats. A large proportion of FSs (>60%) enhanced 7-12 Hz power of the parietal cortex in either with or without ESM injection. Similar response trends existed in both rat strains. Under the condition of no ESM administration, a small portion of trials containing of HVRS discharges was seen during FS in Long-Evans rats but not in Wistar rats. (*D*) Comparison of increased 7-12 Hz powers by FS before and after ESM injection in Long-Evans and Wistar rats. 7-12 Hz powers were significantly enhanced by FS in either with or without ESM administration. Increased 7-12 Hz powers were not significantly reduced by ESM in Long-Evans rats but significantly attenuated in Wistar rats. Similar response patterns were found in both rat strains. #$P < 0.005$; *$P < 0.05$ vs. the baseline by paired *t*-test. +$P < 0.05$ vs. No ESM by paired *t*-test.

1992) (Fig. 3). During HVRS discharges cortical evoked potentials reveal long delays and small magnitudes compared with those in the waking state (Fanselow and Nicolelis 1999; Shaw et al. 2006). Interestingly, temporal portraits of cortical-evoked potentials under HVRS discharges and slow-wave sleep are quite similar (Shaw 2004; Shaw et al. 2006), and subjects usually display unresponsiveness to external stimuli while sleeping. These results support the concept of moderate unresponsiveness to innocuous stimulation during paroxysmal HVRS discharges or SWDs by focal disruption of information processing in specific corticothalamic networks (Blumenfeld 2005). Recently, a study reported that the ability to react to a

TABLE 1. *Comparison of characteristics of spontaneous HVRS discharges and the mu-rhythm-like activity clicited by FS*

	HVRS Discharges	Evoked Mu Rhythm
Dominant frequency	Alpha range	Alpha range
Harmonics	Many	Rare
Magnitude	High	Low
Spatial distribution	Widespread	Local (frontoparietal region)
Occipital activity	Small extent of HVRS activity	FS-related rhythm
Behavior	Whisker twitching	None
Ethosuximide (100 mg/kg ip)	Suppression	Existence in >60% of trials; slight reduction in the occurrence; reduction in alpha power; similar response trends in Wistar and Long-Evans rats

FS, flicker stimulation; HVRS, high-voltage rhythmic spike.

conditioning whisker stimulus showed no difference during normal and HVRS activities (Wiest and Nicolelis 2003). Furthermore, during HVRS activities, rats are preferably associated with task disengagement over total unresponsiveness (Fontanini and Katz 2005). Similar phenomena, i.e., most SWDs are not aborted by nonreinforced stimulation but are significantly stopped by reinforced stimulation of the sound-food conditioning paradigm after training, are also found in WAG/Rij rats (Drinkenburg et al. 2003). These data indicate that HVRS activity is associated with moderate but not total unresponsiveness to mild stimuli of training tasks. Why the animal under a training task reveals a greater ability to react to mild stimulation remains to be resolved. One possibility is that spontaneous HVRS discharges in trained rats may become a non-full-blown absence seizures, so the possibility of unresponsiveness to mild stimulation is reduced. The other possibility is that conditioning paradigm may modify neural networks then lead to a change in the reacting ability. The postulation of neural plasticity is supported by the observations that sensorimotor biofeedback or behavioral reward conditioning is able to reduce seizure frequency in patients with absence seizures (Mirsky et al. 1986).

It is very curious why Long-Evans rats display spontaneous HVRS discharges as observed in several inbred rat strains. This question remains to be answered. Long-Evans hooded rats were developed through crossing Wistar with Brown Norway rats (Lindsay 1979). Brown Norway rats have been demonstrated to be able to stably generate spontaneous SWDs (Crunelli and Leresche 2002; Willoughby and Mackenzie 1992). Moreover, myoclonic whisker twitching is more frequent and of larger amplitude in Brown Norway rats than that seen in other strains (Jando et al. 1995). These results may partially explain why a large portion of hooded rats can generate spontaneous HVRS discharges concomitant with large-amplitude whisker twitching (Nicolelis et al. 1995; Shaw and Liao 2005; Semba et al. 1980).

Numerous evidences described above supports the HVRS discharges in Long-Evans rats being similar to SWDs in GAERS and WAG/Rij rats, which are believed to be absence epileptic models (Coenen et al. 1991; Crunelli and Leresche 2002; Danober et al. 1998). Although the inhibitory effects of three antiabsence drugs on spontaneous HVRS discharges are known to be analogous between Long-Evans and GAERS or WAG/Rij rats, a subtle difference appears in the response of HVRS discharges to CBZ (Marescaux et al. 1984; Peeters et al. 1988) (Fig. 2*B*). The HVRS duration decreased with 10 mg/kg CBZ but little effect was observed at higher dosages. In contrast, the SWD duration was little affected by 10 mg/kg CBZ but was significantly increased at higher dosages (20 and 40 mg/kg) of CBZ in GAERS and WAG/Rij rats. The response curves to CBZ in Long-Evans rats and GAERS or WAG/Rij rats seem to be similar but with a baseline shift. This intrinsic difference in the sensitivity to CBZ may arise from the selective inbreeding of GAERS and WAG/Rij rats with abundant SWDs.

The SWDs of GAERS and WAG/Rij rats are widely accepted as experimental animal models of absence epileptic activity (Coenen et al. 1991; Crunelli and Leresche 2002; Danober et al. 1998; Snead et al. 1999). However, several intrinsic differences exist in these two strains, such as age onset of SWDs, the distribution of D2-like dopamine receptors, amygdala kindling processes, the chromosome locations of gene controlling SWDs, the dose response of intraperitoneal phenytoin injection, and the cortical driving focus of SWDs in pharmacological treatments (see the comparison in the discussion of Gurbanova et al. 2006). These discrepancies may reflect multiple and complicate mechanisms for the generation of SWDs (Crunelli and Leresche 2002). On the other hand, the distribution of HVRS occurrence during wake-sleep states in Long-Evans rats differs from those of WAG/Rij and GAERS rats (Shaw 2004). The dose response of CBZ is also different in three rat strains (Fig. 2*B*) (Marescaux et al. 1984; Peeters et al. 1988). Recently, WAG/Rij rats is demonstrated to display depression-like behavior in forced swim test and to appear inconsistent anxiety-like behavior responses in open field and elevated plus-maze tests (Sarkisova et al. 2003). However, Long-Evans rats showed depression-like behavior during a forced-swim test and displayed consistent low anxiety-like behaviors in both open field and elevated plus-maze tests compared with those of Wistar rats without spontaneous HVRS discharges (unpublished observations). Accordingly, Long-Evans rats may provide an alternative viewpoint about the association between 7-12 Hz high-voltage cortical oscillations and behavioral responses. Because valuable information about the effect of 7-12 Hz HVRS discharges on the brain and behaviors is limited in Long-Evans rats compared with those of GAERS and WAG/Rij rats, the superiority among three experimental models with spontaneous 7-12 Hz high-voltage cortical oscillations remains to be determined.

Although results in the present and previous studies (Coenen et al. 1991; Crunelli and Leresche 2002; Danober et al. 1998; Meeren et al. 2002; Polack and Charpier 2006; Shaw 2004; Shaw and Liao 2005; Snead et al. 1999) suggest that HVRS discharges and SWDs in rats may be associated with absence seizures, the oscillation frequency of HVRS discharges (~9 Hz) differs from the 3-Hz SWDs of absence seizures observed in humans (Mirsky et al. 1986; Niedermeyer 1999b). Previous studies indicated that penicillin and other proconvulsants are unable to induce 3-Hz SWDs in rodents even at higher doses (Avoli 1980; McQueen and Woodbury 1975; Shaw 2004; Snead et al. 1999). Indeed, wave components of HVRS discharges or SWDs are not obvious in rodents (Danober et al. 1998; Shaw 2004; Shaw and Liao 2005; Snead et al. 1999). An absence of wave components in HVRS discharges results in decreasing intervals of two consecutive spikes that leads to an increase in the oscillation frequency. In this respect, the wave durations of SWDs play an important role in the oscillation frequencies of SWDs. The wave component of SWD is primarily contributed by the action of $GABA_B$ receptors (Niedermeyer 1999b; Snead et al. 1999; Staak and Pape 2001). Recently, a change in the dominant action of $GABA_A$ and $GABA_B$ on thalamocortical neurons was demonstrated to cause a shift in the oscillation frequency of SWDs in the computational model (Destexhe 1999) and absence epileptic WAG/Rij rats (Staak and Pape 2001). This may explain why different oscillation frequencies of SWDs exist in humans and rats.

In summary, the present study found a large portion of FSs eliciting small-magnitude mu-rhythm-like activities but not HVRS in both Long-Evans and Wistar rats, which is similar to visual evoked mu rhythm in humans. In addition, effects of

four antiepileptic drugs on HVRS discharges agreed with those observed in absence epileptic patients. In addition to electrophysiological and pharmacological findings about spontaneous HVRS discharges in previous studies (Polack and Charpier 2006; Shaw 2004; Shaw and Liao 2005; Shaw et al. 2006), the present study provides an additional support to the hypothesis that HVRS activity in Long-Evans rats is an absence-like seizure activity rather than the mu rhythm.

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