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The Effect of Generalized Absence Seizures on the Progression of Kindling in the Rat

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Summary: The involvement of the thalamus in limbic epileptogenesis has recently drawn attention to the connectivity between the nuclei of the thalamus and limbic structures. Thalamolimbic circuits are thought to regulate limbic seizure activity whereas thalamocortical circuits are involved in the expression and generation of spike-and-wave discharges (SWDs) in the absence epilepsy models. Genetic Absence Epilepsy Rats From Strasbourg (GAERS) and WAG/Rij (Wistar Albino Glaxo from Rijswijk) are well-defined genetic animal models of absence epilepsy. We aimed to examine the duration of behavioral changes in the kindling process and the relation of SWD activity to the kindling progress in the GAERS and WAG/Rij animals. Electrodes were stereotaxically implanted into the basolateral amygdala and the cortex of rats for stimulation and recording. The animals were stimulated at the threshold for producing afterdischarges. EEG was recorded to analyze SWDs and afterdischarge durations. The seizure severity was evaluated using Racine's 5-stage scale. None of the GAERS animals reached stage 3, 4, or 5 after application of 30 stimulations. The WAG/Rij animals showed different rate of kindling, therefore they were further categorized into the kindling-resistant, slow-kindled, and rapid-kindled groups. The kindling-resistant animals demonstrated a significantly longer duration of SWDs on the first day of the experiment before kindling stimulation and shorter duration of afterdischarge than did the kindled WAG/Rij animals. Behavioral durations at stage 2 were longer in kindled Wistar and WAG/Rij animals compared to kindling-resistant WAG/Rij and GAERS. These results suggest that mechanisms involved in the generation of SWDs act as a counterbalance to the excitability induced by kindling. **Key Words:** Temporal lobe epilepsy model—Absence epilepsy models—GAERS—WAG/Rij—Generalized epilepsy—Kindled.

Childhood typical absence epilepsy involves recurrent episodes of reduced consciousness associated with bilateral spike-and-wave discharges (SWDs) on the cortical EEG (Panayiotopoulos, 1997). During absence seizures, abnormal rhythms are produced by interaction between the thalamus and cortex (Manning et al., 2003). In other words, thalamocortical circuits are involved in the expression and generation of SWDs in human absence epilepsy. In addition to the role of the thalamus as a generator of absence seizure activity, thalamolimbic circuits are thought to regulate limbic seizure activity as well as the physiology of the limbic system. A few studies examining the effect of thalamic stimulation have recently emphasized the involvement of the thalamus in limbic epileptogenesis (Bertram and Zhang, 1999; Bertram et al., 2001). Costimulation of the thalamic reticular nucleus during rapid hippocampal kindling stimulation reduced the number and duration of generalized convulsions, suggesting a role of the thalamic reticular nucleus in the neuronal circuits responsible for limbic seizure generalization (Nanobashvili et al., 2003). Consistent with the results of costimulation of the thalamic reticular nucleus during hippocampal kindling, an amygdala kindling study in an absence epilepsy model, Genetic Absence Epilepsy Rats from Strasbourg (GAERS) showed that GAERS failed to develop stage 3, 4, or 5 even after 30 kindling stimulations (Eşkazan et al., 2002). All GAERS stayed at stage 2 in spite of repeated daily electrical stimulation. The absence of stage 3–5 seizures in GAERS after the maximum number of amygdala stimulations suggests that the thalamic activity may generate the resistance to the secondary generalization of limbic seizures during amygdala kindling. GAERS and WAG/Rij (Wistar Albino Glaxo from Rijwijk) are the

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best-characterized genetic rat models of absence epilepsy (Marescaux et al., 1992; Coenen and van Luijtelaar, 2003). They display spontaneous and reproducible SWDs on EEG and share pharmacological and many clinical characteristics of typical absences in humans (Depaulis and van Luijtelaar, 2005). In the present study, we examined the duration of the behavioral changes during the kindling process and the relation of SWD activity to the kindling progress in the GAERS and the WAG/Rij models. Kindling stimulations were applied to WAG/Rij, GAERS and nonepileptic Wistar animals in the same experimental conditions in block design.

MATERIALS AND METHODS

Experiments were carried out with nonepileptic Wistar control (n = 9), WAG/Rij (n = 13) and GAERS (n = 6) rats, aged 5–12 months. The animals were housed in a temperature-controlled room (20 ± 3°C) with a 12-h light–dark cycle. All animals were allowed free access to commercial rat pellets and tap water. The experimental protocol was approved by the Animal Care and Use Committee of Marmara University (12.2004.Mar).

Surgery

One week before the kindling experiments, the animals were anesthetized with ketamine (100 mg/kg, intraperitoneally [i.p.]) and chlorpromazine (0.5 mg/kg, i.p.). The head of each animal was placed in a stereotaxic instrument (Stoelting Model 51600, Stoelting Co., Illinois, USA). Stainless-steel electrodes insulated except at the tip for stimulation and recording were implanted bilaterally into the basolateral amygdala. All coordinates were obtained from the stereotaxic atlas of Paxinos and Watson (1998) with bregma as the reference point. Stainless steel screws, used for extradural ground and recording electrodes, were placed bilaterally in the skull over frontal and occipital cortex. Electrodes were connected by insulated wires to a microconnector for EEG recordings. All of the electrodes were fixed to the skull with dental acrylic. The animals were allowed to recover from surgery for at least 7 days before the first day of stimulation.

Kindling

On the day of the experiment, the animals were placed singly in Plexiglass cages. Following an hour-long adaptation period, a baseline EEG was recorded for 1 h from all animals. Then, in order to determine the afterdischarge threshold, the right basolateral amygdala (BLA) of the rats was stimulated with an initial stimulation of 50 μA (monophasic, square wave pulses of 80 Hz, each 1 ms in duration, for a total duration of 2 s). This was continued with 50 μA increments until an initial afterdischarge was obtained. Next, the animal was stimulated twice daily at this afterdischarge threshold. Seizure stages observed after each stimulation were classified using Racine's standard 5-stage scale (Racine, 1972): stage 1, facial movements; stage 2, rhythmic head movements, head nodding; stage 3, unilateral forelimb clonus; stage 4, bilateral forelimb clonus and rearing; stage 5, falling and clonic convulsion. The animals were stimulated until they reached a stage 5 seizure state. If the animals did not reach stage 5 with 30 electrical stimulations they were accepted as kindling-resistant. Minimal duration of afterdischarge activity was accepted as a spike discharge lasting 2 s or more immediately after the stimulation (Kelly et al., 2002).

Experimental protocol

Kindling stimulations were applied in the nonepileptic Wistar control, WAG/Rij and GAERS groups. Electrical activity of the stimulated region of the amygdala and cortex was amplified (through BioAmp ML 136) and recorded with a PowerLab 8S System running Chart v.5, (ADI Instruments U.K.) before and after each stimulation.

EEG analysis

Basal EEG was recorded from all Wistar animals to exclude any animal which could have absence-like activity. EEG in all groups was recorded continuously for 1 h before and after the kindling stimulations. Afterdischarge duration was taken to be the total duration of spikes in the EEG recorded from the BLA electrode following the stimulation period.

SWD activity in WAG/Rij and GAERS was determined as previously reported (van Luijtelaar and Coenen, 1986; Vergnes et al., 1990). A SWD complex was identified as such if its duration was at least 1 s with a train of sharp spikes and slow waves (7.5–9 Hz) and amplitude of at least twice the background amplitude of the EEG. The cumulative total duration of SWDs was measured over 10 min periods. "Basal SWD activity" was the mean of the basal cumulative total duration of SWDs before the first five kindling stimulations and "basal afterdischarge duration" was the mean of the durations recorded after the first five stimulations of the kindling process.

Duration of behavioral response after each stimulation was noted as "total seizure duration" independent of the EEG. Total seizure duration was further divided into limbic and motor seizure durations when the animals showed stage 3, 4, or 5 seizures. At these stages limbic seizure duration was the subtraction of motor seizure from the total seizure duration. At stage 1 and 2 limbic seizure duration was equal to the total seizure duration.

Histological verification

Following all experiments, the animals were decapitated to determine electrode placement. The brains were placed in a formalin/sucrose mixture and 40 μm frozen sections were cut in a cryostat and stained with thionin. Only the animals with correct electrode placement (between −1.8 and −3.2 mm from the bregma) were included in the study.

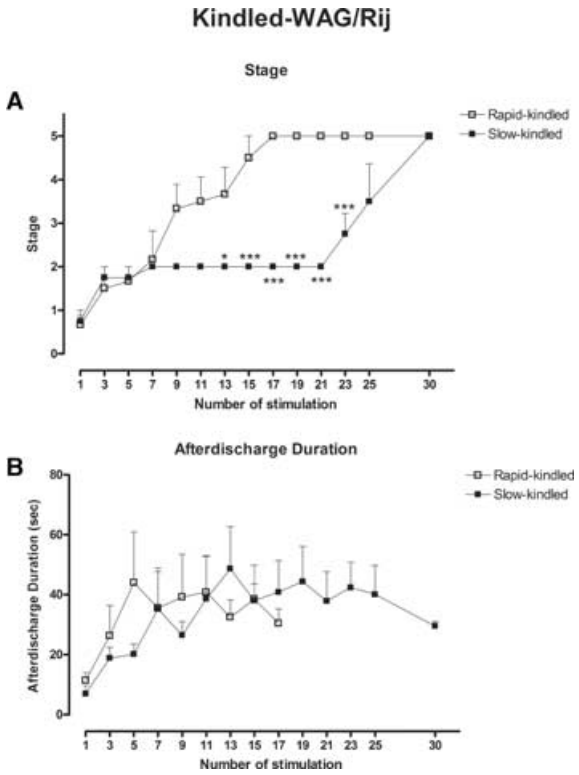

FIG. 1. Seizure stage (**A**) and duration of afterdischarge in the ipsilateral amygdala (**B**) of rapid-kindled (n = 6) and slow-kindled (n = 3) WAG/Rij rats. Data are expressed as mean ± SEM. Two-way ANOVA followed by the post-hoc Bonferroni test revealed significant differences between groups, $^{*}p < 0.05$, $^{***}p < 0.001$.

Data analysis

WAG/Rij rats displaying only stage 2 seizures and not having stage 3, 4, or 5 seizures were referred as the "kindling-resistant" subpopulation of WAG/Rij animals. WAG/Rij rats reaching the stage 5 seizure state were referred as the "kindled" subpopulation of WAG/Rij animals. Further, WAG/Rij animals having a kindling-rate similar to control Wistar group were referred as "rapid-kindled" WAG/Rij and animals that became kindled after the 25th stimulation were referred as "slow-kindled" WAG/Rij.

The results are expressed as "mean ± S.E.M." Data were statistically evaluated by analysis of variance of repeated measures (ANOVA). One-way ANOVA followed by the post-hoc Dunnett test was used to analyze cumulative SWD duration and total, limbic, and motor seizure durations. A two-way ANOVA followed by the post-hoc Bonferroni test was used to compare the kindling rate of WAG/Rij groups. Spearman correlation analysis between basal cumulative SWD duration and kindling rate was performed in kindled (rapid-kindled and slow-kindled WAG/Rij) and nonkindled groups (kindling-resistant WAG/Rij and GAERS). The level of statistical significance was considered to be $p < 0.05$.

RESULTS

Ten out of the thirteen WAG/Rij rats reached the stage 5 seizure state and were referred as the kindled subpopulation of WAG/Rij animals. According to the kindling rates, the kindled-WAG/Rij group was further divided into two subpopulations: rapid-kindled and slow-kindled WAG/Rij (Fig. 1). The rapid-kindled WAG/Rij group (n = 6) showed a similar pattern to Wistar rats in their seizure progression and became kindled by the 17th stimulation whereas slow-kindled WAG/Rij rats (n = 4) reached a stage 5 by the 30th stimulation. On the other hand, three WAG/Rij animals and all GAERS failed to reach stage 3, 4, or 5 and stayed at stage 2 after application of 30 stimulations.

Behavioral durations of total, limbic, and motor seizures observed at first appearance of stage 2, 3, and 4/5 seizure of the Wistar, kindled WAG/Rij, kindling-resistant WAG/Rij, and GAERS groups are summarized in Table 1. Seizure durations were similar between Wistar and kindled-WAG/Rij groups. The total seizure duration at stage 2 was longer in kindled Wistar and WAG/Rij animals compared to kindling-resistant WAG/Rij and GAERS. Post-hoc Dunnett test fallowing one-way analysis of variance revealed significant differences when Wistar group was

TABLE 1. *Behavioral durations of total seizure, limbic seizure and motor seizure observed at first stage 2, 3, and 4/5 seizures*

	Wistar	Kindled-WAG/Rij	Kindling-resistant WAG/Rij	GAERS
Total seizure duration				
Stage 2[a]	34.1 ± 8.8	22.3 ± 2.3	13.7 ± 1.4[b]	11.2 ± 1.0[c]
Stage 3	40.0 ± 7.5	81.8 ± 20.9	–	–
Stage 4/5	45.7 ± 0.7	59.6 ± 13.9	–	–
Limbic seizure duration				
Stage 3	26.3 ± 6.6	57.4 ± 17.2	–	–
Stage 4/5	15.0 ± 3.8	20.3 ± 8.7	–	–
Motor seizure duration				
Stage 3	13.7 ± 0.9	24.4 ± 8.3	–	–
Stage 4/5	30.7 ± 3.9	39.3 ± 9.4	–	–

[a]Total seizure duration at stage 2 is also the limbic seizure duration.
Wistar n = 9, Kindled-WAG/Rij n = 10, Kindling-resistant WAG/Rij n = 3, GAERS n = 6.
Statistically significant differences compared to Wistar group, [b]$p < 0.05$, [c]$p < 0.01$.

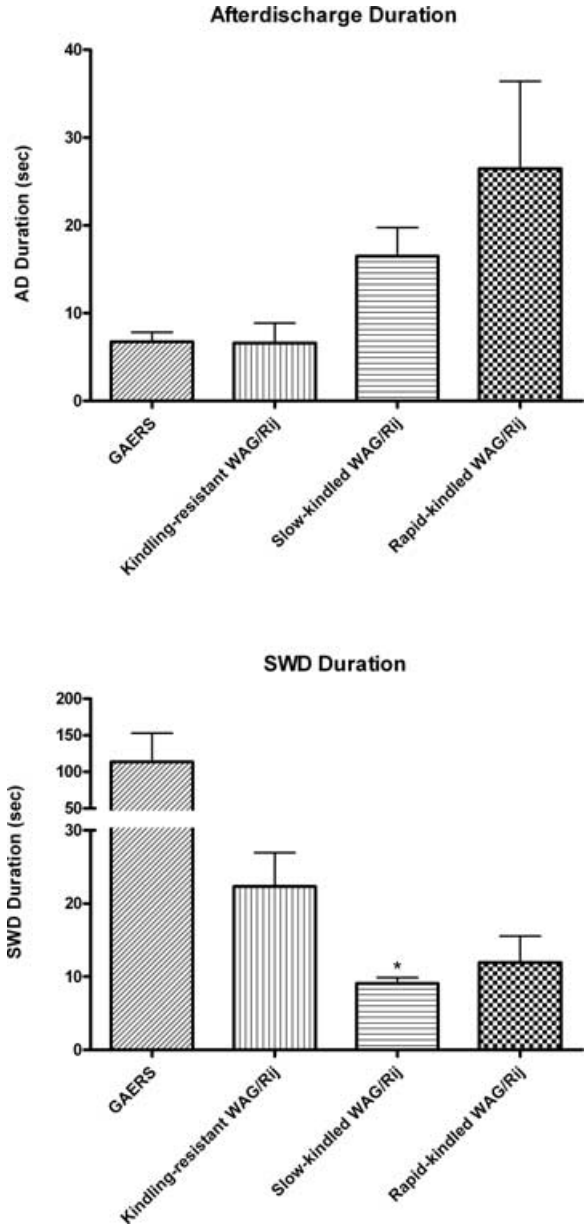

FIG. 2. Afterdischarge duration and basal SWD duration of GAERS (n = 6), kindling-resistant WAG/Rij (n = 3), slow-kindled-WAG/Rij (n = 4), and rapid-kindled-WAG/Rij (n = 6) rats. Data are expressed as mean ± SEM of first five stimulations. *$p < 0.05$, significant difference between GAERS and slow-kindling WAG/Rij compared with repeated measures of one-way ANOVA followed by post-hoc Dunnett test.

compared with kindling-resistant WAG/Rij and GAERS ($p < 0.001$).

Afterdischarge durations and basal SWD durations of the groups showed an opposite tendencies between kindled (rapid-kindled and slow-kindled WAG/Rij) and nonkindled groups (kindling-resistant WAG/Rij and GAERS) (Fig. 2). The mean of the afterdischarge durations following the first five stimulations were higher in the kindled-WAG/Rij groups (rapid- and slow-kindled) than in the kindling-resistant WAG/Rij and GAERS groups (Fig. 2); whereas basal SWD durations were higher in the kindling-resistant WAG/Rij and GAERS groups than the kindled-WAG/Rij animals (Fig. 2). Spearman analysis revealed significant negative correlation between basal cumulative SWD duration and kindling rate in kindled (rapid-kindled and slow-kindled WAG/Rij) and nonkindled groups (kindling-resistant WAG/Rij and GAERS) ($r = -0.789$, $p < 0.001$).

The cumulative total duration of SWDs at the first stage 3 increased significantly for the (0–10 min) poststimulation period when compared with the prestimulation period in the slow-kindled WAG/Rij animals, whereas the cumulative total duration of SWDs at the first stage 2 and 5 in the prestimulation period did not differ from the poststimulation values in the same group (Fig. 3A). The cumulative total duration of SWDs at the first stage 2, 3, or 5 in both the prestimulation and poststimulation periods showed no changes in the kindling-resistant and rapid-kindled WAG/Rij and GAERS groups (Fig 3A and B).

In view of earlier evidence of changing susceptibility to kindling age (de Toledo-Morrell and Morrell, 1991) it is important to report that the GAERS animals were 5–7 months old, the kindling-resistant WAG/Rij animals were 10–12 months old, the slow-kindled WAG/Rij animals were 10–12 months old, and the rapid-kindled WAG/Rij animals were 5–6 months old.

DISCUSSION

In the present study, we aimed to demonstrate whether resistance to kindling in the GAERS model is specific to that particular strain, GAERS, or whether there is a generalization to other comparable rat models of absence epilepsy. GAERS, WAG/Rij, and nonepileptic Wistar animals were stimulated in the same study design until they reached stage 5 or the maximum number of stimulation that was 30 trials. Wistar animals kindled within 14 trials, while 4 out of 13 WAG/Rij rats kindled within 30 trials (the slow-kindled group) and six WAG/Rij animals kindled within 17 trials (the rapid-kindled group). On the other hand, GAERS and kindling-resistant WAG/Rij animals failed to reach stage 3, 4, or 5 seizures. The results of seizure stage and afterdischarge durations of kindling-resistant and kindled WAG/Rij animals were very recently published (Aker et al., 2006). The fact that GAERS and all WAG/Rij groups reached stage 1 and 2 indicates that local events and circuits are activated at the stimulation site triggering the initial phase. Then, WAG/Rij animals exhibit the significant interstrain differences in the number of amygdala stimulations during the kindling progress in terms of stage 3, stage 4, and 5. Therefore, the real interstrain difference in the WAG/Rij animals seems to be in the middle phase that involves predominantly stage 3 seizure manifestations due to forebrain recruitment via

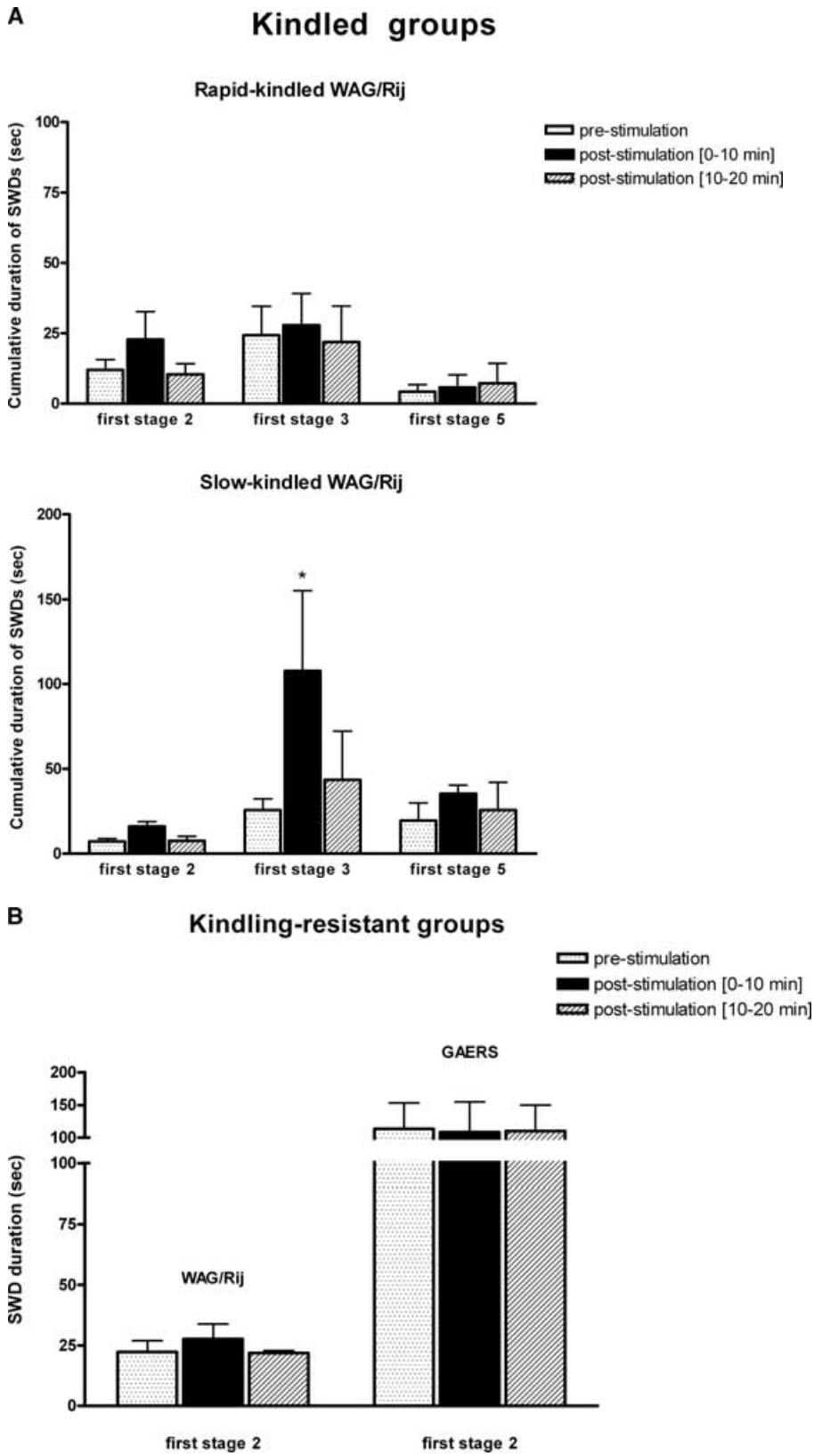

FIG. 3. The cumulative total duration of SWDs at the first stage 2, 3, and 5 in the prestimulation and poststimulation periods of kindled (**A**) and kindling-resistant (**B**) groups. Data are expressed as mean ± SEM. $^{**}p < 0.01$, significant difference between prestimulation and poststimulation periods within the same stimulation interval compared with repeated measures of one-way ANOVA followed by post hoc Dunnett test.

an amygdala-piriform cortex generator and in the generalization process. The amygdala kindling rate correlated positively with the afterdischarge durations of all groups whereas it correlated negatively with the intensity of SWDs. The results are likely to demonstrate that a high level of SWD activity in absence epilepsy reduces the effectiveness of kindling. The thalamic reticular nucleus is the modulator of the thalamocortical activity. Similarly, electrical stimulations in the thalamic reticular nucleus delivered simultaneously with those in the hippocampus induced marked suppression of seizure generalization (Nanobashvili et al., 2003). These results suggest that the thalamic reticular nucleus has links with the limbic structures and may be an important component responsible for limbic seizure circuitries. Although the precise role of the thalamic reticular nucleus is still under debate, it can be postulated that the thalamic reticular nucleus acts to gate dorsal thalamic input to the cerebral cortex (Jones, 1975; Crick, 1984; Guillary and Harting, 2003; Sherman and Guillary, 2005). Meanwhile, it has been suggested both anatomically and electrophysiologically that the thalamus can modulate inhibitory and excitatory transmissions in the structures of the medial temporal lobe (Dolleman-Van der Weel et al., 1997). Stimulation of the midline thalamus in anesthetized rats has been shown to produce the excitatory response in the amygdala and the entorhinal cortex (Zhang and Bertram, 2002).

The finding that the WAG/Rij animals did not show the same level of amygdala kindling resistance as the GAERS model could be explained by different intensities of baseline absence activity in GAERS and WAG/Rij rats. The rate of SWD is higher and cumulative and mean durations are longer in GAERS than those observed in the WAG/Rij model. Likewise, the age of onset of SWD, the distribution of D2-like dopamine receptors and different localizations of absence seizures within the somatosensory cortex are other differences between the GAERS and WAG/Rij models (Danober et al., 1998; Coenen and van Luijtelaar, 2003; Birikouva et al., 2005; Gurbanova et al., 2006). Taken together GAERS and WAG/Rij animals in terms of models of absence epilepsy are not the same. Furthermore, WAG/Rij rats differed significantly in their amygdala kindling rates in the present study. Different susceptibility to amygdala kindling stimulation in the WAG/Rij group might be related to individual differences in the same population. Likewise, Racine and coworkers showed that one subpopulation of Wistar rats is highly susceptible to kindling and the other is resistant (Racine et al., 1999). Then they selectively bred two lines of Wistar rats with different kindling seizure susceptibilities from an original parent population. This selection procedure resulted in seizure-prone and seizure-resistant rat strains based on their speed of amygdala kindling. Moreover, there are also previous studies showing age-related changes in the kindling rate (de Toledo-Morrell et al., 1984; de Toledo-Morrell and Morrell 1991; Chiba et al., 1992). Our results confirm the earlier studies indicating the decreased susceptibility to kindling with aging.

The increase in the cumulative total duration of SWDs at the first stage 3 in the slow-kindled WAG/Rij animals suggests that recruitment of circuitries responsible for stage 3 causes an aggrevation of absence activity. This finding indicates the critical gate between stage 2 and 3 which controls the ability of kindling. The inhibitory activity underlying SWDs may not allow the genesis of the hyperexcitable circuits that consists of the amygdala, the hippocampus, the entorhinal, and piriform cortices. A counterbalance to the excitability induced by kindling may lead to an increase in SWDs.

These results in both GAERS and WAG/Rij animals support the hypothesis in a previous study that vulnerability to seizure activity in any part of the network is influenced by an activity everywhere else in the network, activity in any one part affects activity in all the others. In other words, the decreased susceptibility to kindling in rats with genetic absence epilepsy may be circuit specific.

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