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Corticosterone increases spike-wave discharges in a dose- and time-dependent manner in WAG/Rij rats

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Abstract

Corticosteroids mediate seizure activity in different epilepsy models or epilepsies. However, for childhood absence epilepsy, a nonconvulsive type of epilepsy, direct evidence for corticosteroid seizure modulation is lacking. Thus, in the present study, we analysed the acute systemic effects of different doses of the corticosteroid corticosterone on seizure activity in a well-validated animal model of childhood absence epilepsy, the WAG/Rij rat. We found a time- and dose-dependent increase in the number of spike-wave discharges (SWD) in the EEG, with 500 μg/kg of corticosterone causing a 327% increase in discharges compared to baseline 15–30 min after administration. No treatment effects were found on mean duration of SWD and behavior. Our data indicate that corticosterone in a physiologically relevant dose can aggravate absence seizures in a rapid but transient way. Regarding the time course of the effect, we suggest that corticosterone is acting nongenomically, possibly via a temporary increase of excitatory amino acids.

Keywords: Absence epilepsy; Corticosterone; Corticosteroid hormones; Spike-wave discharges; WAG/Rij rats

1. Introduction

Corticosteroid hormones and related compounds released by the hypothalamic–pituitary–adrenal (HPA) axis have been shown to mediate seizure activity in a variety of epilepsy models and epilepsies. In animal models, corticosteroids increase (Karst et al., 1999; Roberts and Keith, 1995) or decrease seizure activity (Edwards et al., 2002). Patients with temporal lobe epilepsy have been reported to show higher plasma concentrations and secretory rates of adrenocorticotropic hormone (ACTH) and cortisol, compared to controls (Gallagher et al., 1984; Holmes, 1991). Additionally, some forms of childhood epilepsy, such as infantile spasms (West syndrome), Lennox–Gastaut or Landau–Kleffner syndrome, are often treated with ACTH and/or corticosteroids, respectively (Holmes, 1991; Lerman et al., 1991; Mikati et al., 2002; Snead et al., 1983; Tsuru et al., 2000).

However, for childhood absence epilepsy, a nonconvulsive type of epilepsy, characterised by a sudden paroxysmal decrease of consciousness accompanied by behavioural immobility and 3-Hz spike-wave discharges (SWD) in the EEG (Panayiotopoulos, 1999), direct evidence for a possible role of corticosteroids in seizure modulation is rare.

Investigations of therapeutic efficacy and mechanisms for absence epilepsy commonly utilize genetic animal models. Many different strains of rats and mice are prone to develop absence seizures (Burgess and Noebels, 1999; Inoue et al., 1990; Willoughby and Mackenzie, 1992). Animals also show decreased consciousness and immobility during seizures, which is accompanied by vibrissae twitches and accelerated breathing (Danober et al., 1998; Coenen and van Luijtelaar, 2003). The neocortical EEG during an absence seizure in rats is characterised by bilateral generalized synchronous SWD around 8 Hz lasting around 5 s (Danober et al., 1998; van Luijtelaar and Coenen, 1986). Thus, these seizures are analogous to those seen in humans, although the frequency of the trains of SWD in rats and mice are higher than in man (Coenen and van Luijtelaar, 2003).

There are few reports on the involvement of corticosteroids in the mediation of absence seizures. (1) DBA/2J mice show spontaneous spike-wave spindling episodes (7–8 Hz) in their neocortical EEG (Capasso and Loizzo, 2003;

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Ryan, 1984) that can be reduced by dexamethasone, corticotrophin-releasing hormone, adrenocorticothrophic hormone and corticosterone (Capasso et al., 1994). As well, the application of a glucocorticoid receptor antagonist increases discharges (Capasso et al., 1994). (2) In a recent study, de Bruin et al. (2000) compared four rat strains (APO-SUS, WAG/Rij, APO-UNSUS and ACI) with respect to their amount of SWD. While SWD were abundantly present in the first two strains (APO-SUS and WAG/Rij), they were less pronounced or nearly absent in the latter two (APO-UNSUS and ACI). Interestingly, these strains also differ in HPA-axis activity. (3) Rots et al. (1995) demonstrated that APO-SUS rats (high amount of SWD) had higher basal ACTH plasma levels and lower free corticosterone plasma levels compared to APO-UNSUS rats (low amount of SWD). Together, these data (2 and 3) suggest a relationship between basal levels of corticosteroid hormones and SWD in rats. A recent study by Tolmacheva et al. (2003) underlines this assumption. (4) Tolmacheva et al. (2003) used ACI rats, a strain nearly devoid of SWD and therefore often used as nonepileptic control, and WAG/Rij rats, a valid animal model of absence epilepsy (Coenen and van Luijtelaar, 2003). They found that ACI rats had higher basal ACTH and corticosterone plasma levels compared to WAG/Rij rats. Furthermore, within WAG/Rij rats, a negative correlation between the number of SWD and basal ACTH and corticosterone plasma levels was found, lending additional support for a relationship between plasma levels of corticosteroids and SWD in rats (Tolmacheva et al., 2003).

The aim of the present experiment was to further investigate the possible role of corticosteroids in mediating absence seizure activity. The dose-dependent effects of the glucocorticoid hormone corticosterone (250 and 500 μg/kg) compared to vehicle or no injections on the number and mean duration of SWD in WAG/Rij rats were examined.

2. Materials and methods

2.1. Animals and surgery

Adult male WAG/Rij rats, bred and born in the laboratory of Nijmegen University, were used. All experimental manipulations were approved by the local animal ethical committee of Nijmegen University and in accordance with local guidelines and the European Communities Council Directive of 24 November 1986 (86/609/EEC). All rats were group housed (two to three animals per cage) until surgery. After surgery, rats were single housed. Standard rat chow (Hope Farms, Woerden, The Netherlands) and fresh tap water were provided ad libitum. Animals were maintained on a reverse 12-h light/dark cycle (white light on at 1700 h).

Around 9 to 10 months of age, rats underwent surgery for electrode implantation. Anaesthesia was induced with 4.5% isoflurane and rats received 0.1 ml atropine sulphate intramuscularly as parasympatholyticum to prevent excessive salivation. Rats were mounted in a stereotactic frame (Kopf Instruments, Tujunga, CA, USA) and maintenance anaesthesia was provided by permanent isoflurane inhalation (2.5–3%) via a nose mask. Anaesthetic depth was controlled by the hindlimb withdrawal reflex. The body temperature was monitored and kept constant with a heating pad. Rats were implanted with unilateral epidural electrodes (Plastic One MS-332/2-A, Roanoke, VA, USA) over the frontal (A–P: 2.0; M–L: − 3.5) and parietal (A–P: − 6.0; M–L: − 4.0) cortex. An electrode placed over the cerebellum served as ground. All coordinates were determined according to Paxinos and Watson (1998) (Bregma zero–zero, skull surface flat). The electrode socket was fixed to the skull using two stainless steel jewellery screws and dental acrylic. Rats were allowed to recover for at least 1 week prior to testing.

2.2. EEG/SWD and behavioral recordings

For recordings, rats were placed in transparent Plexiglas cages (25 × 30 × 35 cm) and connected to EEG leads via a swivel that allowed free movement. The signals were amplified and filtered (1–100 Hz), digitised (sampling rate 512 Hz) and saved on disk for subsequent off-line analysis using a microcomputer and a Windaq system (DATAQ Instruments, Akron, OH, USA). To prevent any putative confounding novelty effects on EEG recordings, the rats received a 1-day habituation to the recording situation. Food and tap water were made available ad libitum throughout the experiment. During recordings, rats were exposed to background white noise (53.2 dB). The EEG was recorded during the dark phase between 1000 and 1300 h, when basal plasma levels of corticosterone are fairly low and stable (Atkinson and Waddell, 1997), and SWD are quite high (van Luijtelaar and Coenen, 1988). SWD were automatically detected by SWC-finder and visually verified afterwards by one of the authors using criteria described earlier (van Luijtelaar and Coenen, 1986). Number and mean duration of SWD were determined for 15-min intervals. The average number and mean duration of SWD during the baseline EEG were calculated. Postinjection scores for number and mean duration of SWD were calculated as percentage of baseline per interval.

Given the close relationship between SWD and vigilance levels (Coenen et al., 1991; Drinkenburg et al., 1991), we also recorded the behavior of the rats on video for off-line analysis. In line with criteria described elsewhere (van Luijtelaar et al., 1996), explorative (sniffing, rearing, walking, digging and manipulating objects with the forepaws), automatic (grooming, eating, drinking, licking and defecation) and passive (sitting, standing or lying still and sleeping) behaviors were scored from video for the 2-h postinjection period by use of a Tandy 102 and The Observer for postprocessing (Noldus, 1991). The total duration (in seconds) of each behavior was determined per 15-min postinjection interval.

2.3. Corticosterone injections

For corticosterone injections, ready-made corticosterone HBC (2-hydroxypropyl-β-cyclodextrin) complex (Sigma-Aldrich RBI, Zwijndrecht, The Netherlands) was dissolved in saline, while vehicle consisted of only HBC complex (Sigma-Aldrich RBI) dissolved in saline. The drugs were injected in a dose of 1 ml/kg. After 1-h baseline EEG recordings, rats were either left completely undisturbed (control) or received an intraperitoneal injection of vehicle, 250 or 500 μg/kg corticosterone complex at 1100 h. EEG recordings continued for 2 h postinjection. We included a group that received no injections to control for a possible increase of endogenous corticosteroids and related stress hormones caused by the handling/injection stress itself, thereby blurring possible effects of corticosterone injections.

2.4. Statistical analyses

Statistical analyses were performed using SPSS 11.5 for Windows. The between factor in all analyses was treatment condition (control, vehicle, and 250 and 500 μg/kg corticosterone). The dependent variables (number and mean duration of SWD during baseline, number or mean duration as percentage of baseline per postinjection interval, or total duration of explorative, automatic or passive behavior) were analysed by ANOVA or MANOVA (Pillai's Trace Test) with or without repeated-measurements factors. Possible factorial interactions were further analysed by ANOVA and MANOVA. Analyses were followed by Scheffé post hoc test, if appropriate. A P value of .05 was regarded as significant.

3. Results

3.1. General

All rats showed SWD, independent of treatment condition. Fig. 1 displays an example of a typical SWD as recorded in WAG/Rij rats. An SWD was characterised by an ongoing pattern of 7- to 8-Hz asymmetric sharp spikes of positive deflection, followed by a slow wave. The amplitude of a spike was at least twice the background EEG activity.

3.2. Effects of corticosterone on number and mean duration of SWD

The number and mean duration of SWD were comparable to those generally observed in WAG/Rij rats of this age. No differences between treatment conditions were found for number of SWD [$F(3,43)=2.13$, $P=.11$] and mean duration of SWD [$F(3,43)=0.42$, $P=.737$] during baseline.

Fig. 2a gives an overview of the results for number of SWD as percentage of baseline for the 2-h postinjection period across the four groups. The MANOVA revealed an overall effect for treatment condition [$F(24,144)=1.66$, $P<.05$]. Significant differences between treatment conditions were found between 15 and 30 min [$F(3,43)=5.97$, $P=.002$] and between 60 and 75 min [$F(3,43)=2.94$, $P<.05$] postinjection interval. Scheffé post hoc test showed that rats that received 500 μg/kg corticosterone showed a significant increase of SWD during the 15- to 30-min interval compared to control and vehicle-treated rats. Rats that got 500 μg/kg corticosterone showed a threefold (327%) increase of SWD compared to baseline. Rats that received 250 μg/kg corticosterone also showed an increase of SWD, albeit not significant. During the 60- to 75-min interval, Scheffé post hoc test did not show any differences between treatment conditions.

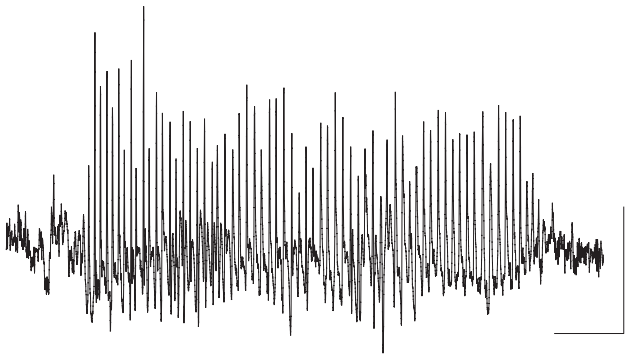

Fig. 1. A typical SWD of a WAG/Rij rat. SWD were characterised by an ongoing pattern of 7- to 8-Hz asymmetric sharp spikes of positive deflection, followed by a slow wave. The amplitude of a spike was at least twice the background EEG activity. Scale bars indicate time 1 s (abscissa) and amplitude 1 mV (ordinate).

Fig. 2b gives an overview of the results for mean duration of SWD as percentage of baseline for the 2-h postinjection period across the four groups. In contrast to number of SWD, no differences between treatment conditions were found for mean duration of SWD during any of the postinjection intervals.

3.3. Effects of corticosterone on behavior

Fig. 3 depicts the results of the behavioral scorings during the 2-h postinjection period. The repeated-measurements MANOVA revealed an effect for behavior [$F(2,42)=102.02$, $P<.001$] and a Time × Behavior interaction effect [$F(14,30)=13.77$, $P<.001$]. No effects were found for treatment condition. Further analysis of the Time × Behavior interaction effect revealed a time effect for explorative [$F(7,40)=9.61$, $P<.001$], automatic [$F(7,40)=4.78$, $P<.001$] and passive [$F(7,40)=16.14$, $P<.001$] behaviors. The first two behaviors generally decreased over time, while passive behavior showed an increase. Significant differences between behavioral categories were found over the intervals, with automatic>passive/explorative during the 0- to 15-min [$F(2,45)=4.28$, $P<.05$] interval; passive>automatic>ex-

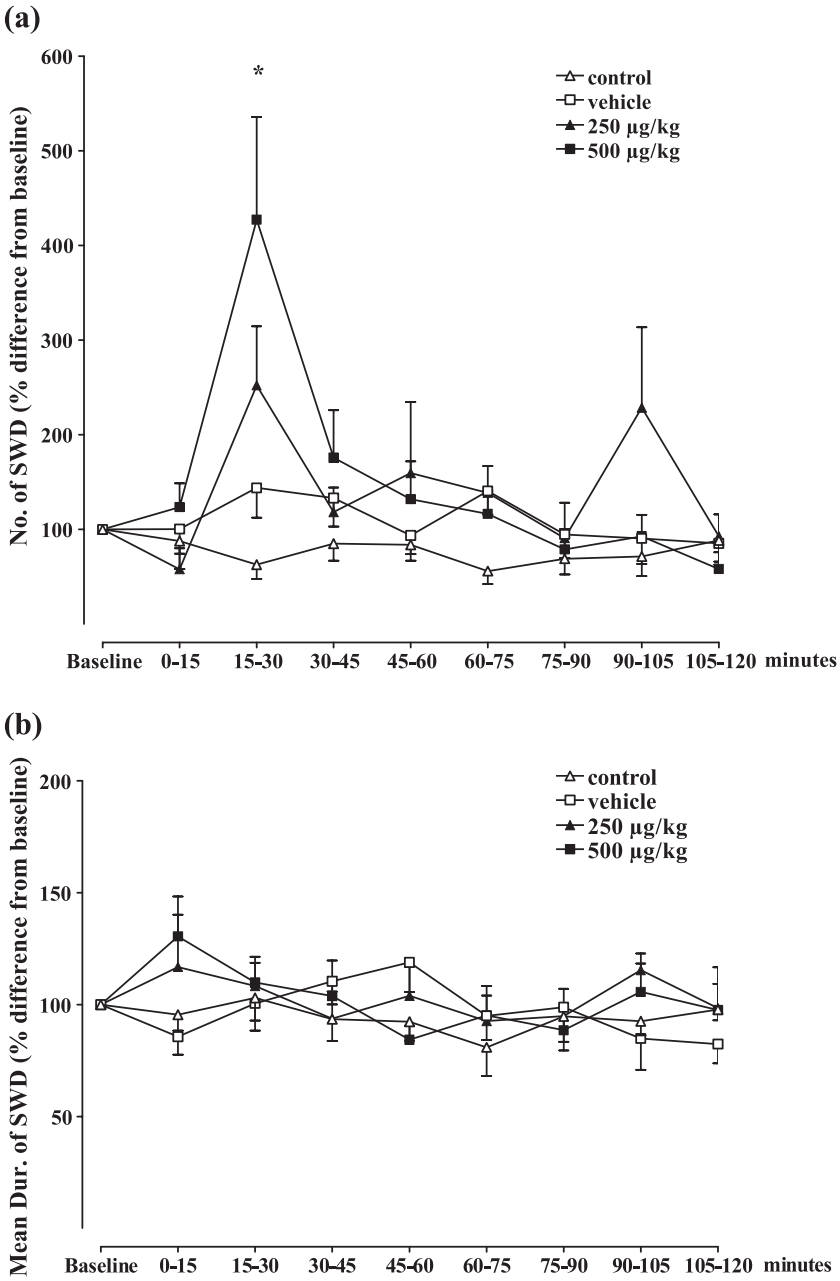

Fig. 2. Effects of corticosterone on number (a) and mean duration (b) of SWD as percentages of baseline over the 2-h postinjection period. Baseline values were set to 100% for graphical impression only. Data represent mean ± S.E.M. per 15-min interval. For number of SWD (a), $*P$=.002 indicates significant differences between treatment conditions during 15–30 min postinjection: rats that received 500 µg/kg corticosterone showed a significant increase of SWD compared to control and vehicle-treated rats. No differences between treatment conditions were found for mean duration of SWD (b).

plorative during the 15- to 30-min [$F(2,45)=37.34$, $P<.001$], 30- to 45-min [$F(2,45)=60.33$, $P<.001$], 45- to 60-min [$F(2,45)=81.54$, $P<.001$], 90- to 105-min [$F(2,45)=31.26$, $P<.001$] and 105- to 120-min [$F(2,45)=24.43$, $P<.001$] intervals; and passive>automatic/explorative during the 60- to 75-min [$F(2,45)=46.6$, $P<.001$] and 75- to 90-min [$F(2,45)=20.66$, $P<.001$] intervals.

4. Discussion

The aim of the present study was to reveal if corticosteroids mediate seizure activity in a valid animal model of absence epilepsy, the WAG/Rij rat. Our data demonstrate for the first time that the corticosteroid hormone corticosterone influences seizure activity in WAG/Rij rats in a dose- and time-dependent manner.

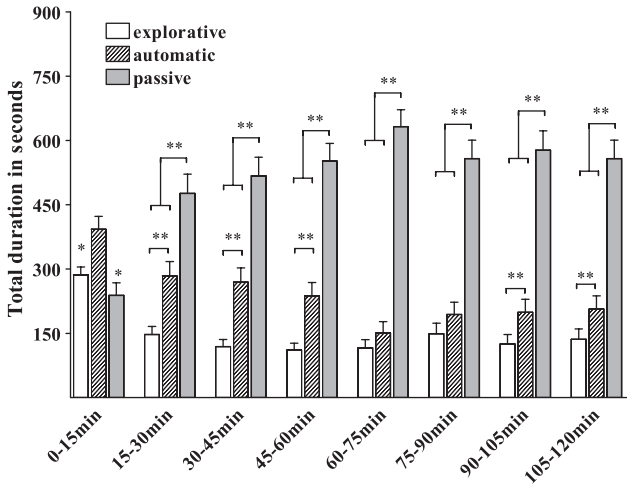

Fig. 3. Behavioral scores over the 2-h postinjection period. Data represent total duration in seconds (mean ± S.E.M.) per 15-min interval. Because treatment condition had no effects, the behavioral data of the four groups were pooled. $*P<.05$, $**P<.001$ indicates differences between behavioral categories.

Corticosterone administration resulted in a rapid and transient increase in number of SWD between 15 and 30 min after injection, with rats receiving 500 μg/kg showing a threefold (327%) increase of SWD. Rats that received either no or vehicle injections showed comparable amounts of discharges across all intervals. We found no effect of treatment condition on seizure duration, however. The different effects on number and mean duration of SWD suggest that they are independent factors mediating seizure activity. This is in line with other studies, showing that number and mean duration of SWD are controlled by different genes (Peeters et al., 1990a, 1992) and react differently to environmental manipulations (Schridde and van Luijtelaar, 2004) or to certain drugs (van Luijtelaar and Coenen, 1995).

The effect on number of SWD could not be ascribed to handling/injection stress in general, because vehicle-treated rats, receiving an equal amount of handling/injection stress as rats receiving corticosterone, did not differ from the control rats that were left undisturbed. However, rats that also received corticosterone showed an increase of SWD, and rats from the 500 μg/kg group had even significantly more SWD compared to vehicle-treated rats.

SWD show an intimate relationship with behavior, being more prominent during states of drowsiness and inactivity, while being mostly absent during active states (Coenen et al., 1991; Drinkenburg et al., 1991). We therefore scored behavior during the 2-h postinjection period to control for possible confounding influences on SWD caused by treatment condition induced behavioral changes. Although we found a behavior and a Time × Behavior interaction effect, we found no effects of treatment condition on behavior, showing that behavior cannot account for the observed increase of SWD. Except during the first 15 min, when automatic behavior dominated, the rats were mostly passive. The dominance of passive behavior during this time of day is in line with circadian behavioral patterns observed in WAG/Rij rats (van Luijtelaar and Coenen, 1988). The transient increase of activity shortly after injection might have been caused by the drug and/or handling/injection itself. Handling a rat can induce automatic behaviors, such as grooming (van Erp et al., 1994) and hormones of the HPA axis as ACTH are known for their grooming-inducing properties (van Erp et al., 1991).

The increase of SWD by corticosterone in our study is in contrast to what has been found in DBA/J2 mice. In these mice, corticosterone reduced spontaneously occurring spike-wave spindling episodes (Capasso et al., 1994). However, in DBA/J2 mice, the effects of corticosterone on paroxysms showed a time lag of 30–60 min and could be prevented by a protein synthesis inhibitor, whereas antagonism of the cytosolic glucocorticoid receptor by RU-38486 increased SWD. This suggests a genomic mechanism of corticosterone on SWD (Capasso et al., 1994). In our study, SWD increased between 15 and 30 min postinjection and returned to baseline levels thereafter. This time course is generally too fast for a genomic-mediated effect of corticosterone, which normally requires 30 min, hours or even days (Borski, 2000). Next, the acute application of RU-38486 had no effect on SWD in WAG/Rij rats (van Luijtelaar et al., 2001).

At first glance, our results also differ from the negative relationship between basal plasma levels of corticosterone and number of SWD as reported for WAG/Rij rats by Tolmacheva et al. (2003). Regarding this correlation, one would predict that increased concentrations of corticosterone would decrease SWD. Obviously, this was not found. This disagreement might be caused by the different time points of measurements. Tolmacheva et al. (2003) collected their data during the first hours of the dark phase (reverse 12-h light/dark cycle; lights out at 0830 h), between 0900 and 1400 h when corticosterone plasma levels are rather high and variable, while in the current experiment, measurements were performed towards the end of the dark phase when levels are lower and more stable. It can also not be excluded that the negative correlation between corticosterone and SWD reported by Tolmacheva et al. (2003) might be due to underlying covariant variables (e.g., behavior differences) between rats. Another possibility is that the effects of an acute application of corticosterone on SWD as in our study are due to a nongenomic action of corticosterone, while the basal levels of corticosterone influence SWD through genomic pathways, which have an opposite relationship with SWD activity, as was demonstrated in DBA/2J mice (Capasso et al., 1994).

The time course of corticosterone to produce rapid, but short-lasting, increases in SWD suggests a nongenomic mechanism of action. Various nongenomic corticosteroid binding sites and mechanisms have been proposed (Makara and Haller, 2001). However, only those mechanisms that

can be linked to known pathogenic processes in SWD will be discussed here.

The aggravation of absence seizures by corticosterone corresponds to effects of neurosteroids, another class of steroids closely related to corticosterone. Progesterone led to a rapid increase of SWD in WAG/Rij rats through its active metabolite allopregnanolone (van Luijtelaar et al., 2001; Budziszewska et al., 1999; van Luijtelaar et al., 2003), a positive allosteric modulator of GABA-A receptors (Majewska et al., 1986). GABA-A receptors play a critical role in SWD: GABA-A mimetics increase SWD in WAG/Rij rats (Peeters et al., 1989).

Also, corticosteroids can influence GABA functioning nongenomically. Using synaptosomal membranes prepared from rat brains, Majewska et al. (1985) could show that binding of the GABA agonist muscimol or the antagonist TBPS (Majewska, 1987) was enhanced by corticosteroids in physiologically relevant concentrations. However, at present, it is not definitely clear via which nongenomic binding sites or mechanisms corticosterone rapidly mediates GABA functioning (Makara and Haller, 2001).

Recently, it was shown that the systemic administration of corticosterone led to a rapid and transient increase of extracellular glutamate and aspartate levels (Venero and Borrell, 1999). This increase could not be prevented by protein synthesis inhibitors or intracellular corticosteroid receptor antagonists, suggesting a nongenomic mechanism of the action of corticosterone. The time course of the rise and fall of the excitatory amino acids, an increase within 15 min, peaking around 25 min and returning to baseline after 35 min, is parallel to our observed rise and fall of SWD. Glutamate and aspartate have been shown to influence SWD. The application of NMDA (Peeters et al., 1990b) or AMPA (Peeters et al., 1994) led to a dose-dependent increase of SWD in WAG/Rij rats. Interestingly, the effects were limited to the number of discharges, without influencing their duration. Also, in the present study, we found that corticosterone led to an increase of SWD, while seizure duration was not affected.

In summary, we found that corticosterone in a physiologically relevant dose can aggravate absence seizures in a rapid but transient way. Regarding the time course of the effect, we suggest that corticosterone acts via a nongenomic way, possibly affecting SWD by a temporary increase of excitatory amino acids.

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