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The sleep-wakefulness cycle of Wistar rats with spontaneous absence-like epilepsy

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ABSTRACT. Possible interactions between the sleep-wakefulness cycle and a new kind of spontaneous epilepsy, expressed as absence-like seizures and spike-wave bursts in FMUSP rats, are evaluated. The electro-oscillograms of some cortical and subcortical regions of the brain were recorded, as well as head, rostrum/vibrissae and eye movements. Recordings were performed uninterruptedly during 24 hours. The seizures were mostly concentrated in the wakefulness state but they could occur in any other phase, including paradoxical sleep. After the seizure, the rats usually returned to the same phase that was interrupted, although they often returned to wakefulness. There was an intense fragmentation of the sleep-wakefulness cycle. The incidence of each cycle phase was significantly reduced, except S_{III} of synchronized sleep and paradoxical sleep, thus maintaining the overall duration and architecture of the sleep-wakefulness cycle. The fragmentation of the cycle seems to be due to an impairment of the very processes that generate sleep and wakefulness. Electrophysiological and behavioral profiles of the FMUSP rats recommend accurate and comprehensive study of the animal model owing to its resemblance to seizures in humans and also to discrepancies with existing genetic or experimental epilepsy models.

Keywords: epilepsy, absence seizures, spike-wave, sleep, wakefulness, rats.

O ciclo vigília-sono de ratos Wistar portadores de epilepsia espontânea tipo ausência

RESUMO. A razão principal desta investigação foi estudar a arquitetura do ciclo vigília-sono numa cepa de ratos Wistar (FMUSP-rats) portadores de epilepsia espontânea tipo ausência. Foram utilizados 10 ratos Wistar adultos, que receberam eletrodos em regiões corticais e subcorticais, nos músculos trapézios e nos epicantos oculares, pelos quais registramos os eletroscilogramas continuamente por 24 horas, dos quais foram analisados os registros eletroscilográficos e demais parâmetros da arquitetura do ciclo vigília-sono. As crises ocorriam preferencialmente durante o período escuro, coincidindo com a maior prevalência de estados de vigília. O ciclo vigília-sono sofreu intensa fragmentação nos ratos epilépticos, e a duração média de algumas fases do sono foi mais prolongada nos ratos epilépticos do que nos sadios. As manifestações eletrofisiológicas das crises assumiram várias formas, predominando, porém, os complexos espícula-onda (de 7 a 9,5 Hz) o que se assemelha muito à faixa de oscilação das ondas teta. As características eletrofisiológicas e comportamentais da epilepsia que estudamos recomendam o estudo acurado e abrangente desse modelo de síndrome epiléptica, por sua semelhança com as crises encontradas em humanos, mas também por algumas discrepâncias em relação a modelos de epilepsia genética ou experimental já existentes.

Palavras-chave: epilepsia, crises de ausência, espícula-onda, sono, vigília, ratos.

Introduction

Epilepsy's interaction with biological rhythmicity has been known for centuries. The relationship between clinical seizures and the sleep-wakefulness cycle is complex and clinically relevant (QUIGG, 2000). Epileptogenic discharges are known to be influenced by the sleep-wakefulness cycle and vice-versa (BAZIL; WALCZACK, 1997). Such interactions are expressed as changes in the epileptic pattern, in interictal activity, in sleep structure and psychological activities at daytime, while several studies have demonstrated that sleep seems to facilitate epileptic seizures (SHOUSE et al., 1996; SZYMUSIAK et al., 1996). Since sleep is as a rule electroencephalographically expressed as synchronization, the electrophysiological pattern probably favors epileptogenesis (BAZIL; WALCZACK, 1997), while desynchronized sleep suppresses generalized epileptiform discharges and shows variable effects on focal discharges

(NEGRILLO, 2013). Primary or secondary tonic-clonic seizures occur preferentially during synchronized sleep (SHOUSE et al., 1996; DRAKE et al., 1990). Clonic (TASSINARI et al., 2009) and temporal and frontal lobe epilepsy often interrupt sleep as soon as it starts (QUIGG, 2000).

Contrastingly, some seizures are produced immediately after awakening (*awakening seizures*), including short-lasting myoclonus with secondary generalization (tonic-clonic seizures), generalized clonic seizures and, albeit infrequent, absence seizures (PELED; LAVIE, 1986). Typical absence seizures in humans occur predominantly during wakefulness, despite spike-wave discharges do sometimes occur at the onset of sleep and/or during periods of somnolence (HALÀSZ, 1972; 1981; MONTPLAISIR et al., 1985). Therefore, as expected, the sleep-wakefulness cycle is highly influenced by epileptic seizures. In fact, it is well known that sleep latency is increased by the presence of epilepsy, coupled to an augmentation of the frequency and duration of nocturnal awakenings and, consequently, sleep fragmentation, superficialization of sleep due to reduction of synchronized sleep phases III and IV and increase of phases I and II. Paradoxical sleep may be fragmented and/or reduced by the seizures, albeit with no rebound. Increase in diurnal somnolence is common due to sleep fragmentation. As a consequence of epileptic seizures, sleep may be entirely impaired or even absent. In patients with primary or secondary seizures, the EEG may be so abnormal that sleep phases become impossible to characterize. Sleep phases in some patients are extremely modified, either increased or decreased, to the point that it may be impossible for the patients to pass from one sleep phase to another (TASSINARI et al., 1988; SHOUSE et al., 1996; QUIGG, 2000).

Several studies have demonstrated that the thalamo-cortical circuits are involved in generating spike-wave complexes and sleep spindles, suggesting that the mechanisms involved in both electrophysiological phenomena are at least partially the same (AVANZINI et al., 2000; FUTATSUGI, RIVIELLO, 1998; KANDEL, BUSZÁKI, 1997; KELLAWAY et al., 1980; KOSTOPOULOS, 2000). This relationship may be involved in the interference of epilepsy on sleep, mainly on synchronized sleep.

Over a hundred models of experimental or spontaneous epilepsy in animals were introduced in the literature during the past three decades. Such models are of the utmost relevance in studying not only the manifestations of epilepsy but mainly its mechanisms and even treatment. Of course, the convenience of studying epilepsy in such animals is the possibility of using invasive techniques (McGONIGLEA, RUGGERI, 2014; WENDLER, WEHLING, 2010) that help understand basic mechanisms related to epileptic seizures (JEFFREYS, 2003), the discovery and development of new antiepileptic drugs and shed some light on possible specific efficacies of the compound against different types of seizures or epilepsy (LÖSCHER, 2011).

The interactions between seizures and sleep have been experimentally studied in different kinds of epilepsy, such as that produced in cats by penicillin (SZYMUSIAK et al., 1996), in rats by pilocarpine (CAVALHEIRO et al., 1991), kainic (HELLIER, DUDEK, 1999) and domoic acids (DAKSHINAMURTI et al., 1991) in Wistar rats with genetic types of spontaneous absence seizures, such as the GAERS (DANOBER, et al., 1993) and WAG/Rij lineage (DRINKENBURG et al., 1993). In general, the main reason for such studies has been the investigation of epilepsy throughout the different phases of the sleep-wakefulness cycle.

In current assay, the interaction between the sleep-wakefulness cycle and seizures in a strain of Wistar rats labeled FMUSP rats (acronym of Faculty of Medicine, University of São Paulo) with spontaneous, probably atypical, absence-like epilepsy with spike-wave discharges was investigated (ANDRÉ et al., 2014).

Material and methods

Experimental groups: Five healthy and five epileptic adult male Wistar rats (3 months old, weighing 230–400 g) were selected. In previous recordings, the rats revealed either normal electro-oscillograms or spontaneous absence seizures and spike-wave discharges in several areas of the brain. Animals were housed in individual cages in an isolated room at a constant temperature of 22°C, with 12-h photoperiod (light period from 7h00 am to 7h00 pm) and free access to food and filtered water. Current experiment was approved by two ethical committees (UNIFESP, protocol n. 1255/00, and CAPPesq-HC-USP, protocol n. 197/00).

Surgical procedures: Rats were anesthetized with 150 mg kg^{-1} ketamine chlorohydrate (Ketalar$^{(R)}$) plus Diazepam (0.1 mL kg^{-1}) i.p. administration to record the electrical activity of the brain (EEG). Bipolar NiCr electrodes (160 µm in diameter), entirely insulated except at the end cross section, were bilaterally implanted over neocortical areas 10 (AP=+3.0; L=2.5), 3

(AP=-1.5; L=3.0) and 17 (AP=-6.0; L=3.5) [42-44] and on the hippocampal CA_1 (AP=-3.0; L=1.5; H=-3.0) and CA_3 (AP=-3.3; L=2.5; H=-3.8) fields, in the lateral geniculate nucleus (AP=-4.3; L=1.6; H=-4.8), in the basolateral nucleus of the amygdala (AP=-2.8; L=5.0; H=-8.5) and in the thalamic reticular nucleus (AP=-1.4; L=1.6; H=6.0), following stereotaxic coordinates (PAXINOS; WATSON, 1997). Not all the leads were recorded in each experiment (Figure 1). For actigraphic recordings, electrodes were implanted in the trapezius muscles, in the muscle pad that moves rostrum+vibrissae and in the lateral epicanthus of each eye to record head, rostrum+vibrissae and eye movements, respectively.

EEG and behavioral recordings: Recording sessions were carried out following seven days after electrode implantation (21-channel Nihon-Kohden mod. Neurofax EEG 4400 instrument). All animals were subjected to a 24-h continuous recording. The configuration used was: calibration pulse = 50 μV, EEG time constant = 0.3 s, actigraphic time constant = 0.001 s, 30 Hz low-pass filter (EEG leads), 120 Hz low-pass filter (actigraphic leads) and notch filter for 60 Hz attenuation. For quantitative analysis, signals were recorded in parallel by a high-resolution spectral analyzer, 0-128 kHz, 16 output channels, coupled to a IBM-PC compatible machine. Identification of the phases and states of the wakefulness-sleep cycle followed well tested EEG and actigraphic criteria (VALLE et al., 1992). Concomitant with the EEG and actigraphic recordings, behavioral changes were identified through visual observation and annotated on-line on the recording paper.

Data analysis: Behavioral and EEG data were electronically stored and later analyzed off-line (Statistica 5.0, Statsoft, Inc.). A descriptive statistics was used to calculate the mean, standard error of the mean and percentage of each phase of the wakefulness-sleep cycle and of the spike-wave bursts for each animal. Student's *t* test was employed for data comparison, at 5% significance level ($p < 0.05$). Additionally, samples lasting 10 seconds were collected from all the stages of the wakefulness-sleep cycle, off-line subjected to Fourier (FFT) analysis, and then were compared to find out similarities or discrepancies among the EEG of the areas from which they were recorded, as well as between the control and the epileptic group.

When the experiments were completed, the animals were killed by an overdose of the default anesthetic and the position of each subcortical electrode was checked on Nissl stained sections of the brain.

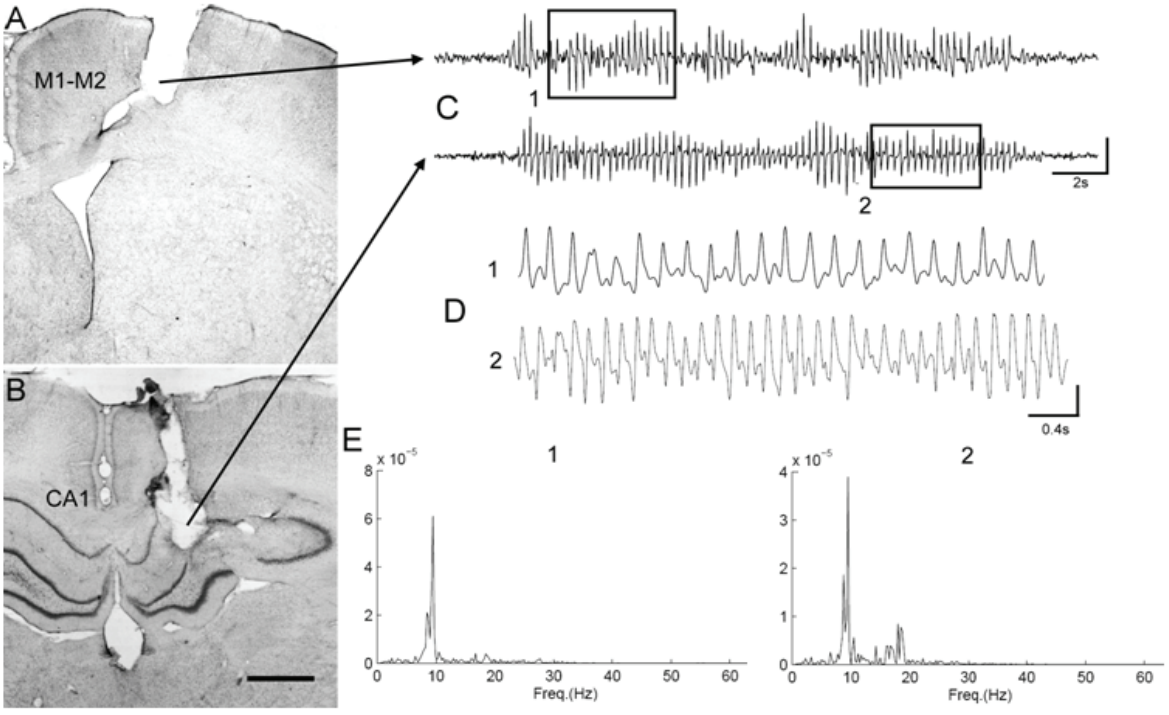

Figure 1. Photomicrographs (A and B) of Nissl-stained (thionin) frontal sections of the rat's brain, showing the recording sites examined. A: primary/secondary motor cortex (M1-M2). B: CA1 field of the hippocampus (CA1). Scale Bar = 1 mm. C and D) Spike-wave bursts characteristic of FMUSP-rats, occurring simultaneously in A10 (upper tracing) and in CA1 (lower tracing). Vertical calibration bar: 100 μV. E) Frequency spectra (FFT) of 10 pooled epochs (2 s each) per animal of A10 (1) and CA1 (2) EEG.

Results

Wakefulness in rats may be clearly identified as relaxed and attentive (VALLE et al., 1992; URSIN, 1968). In relaxed wakefulness, motor activity is low or almost absent and the electro-oscillograms show slow and irregular theta waves in most neocortical areas and in hippocampus. In attentive wakefulness, area 10 is desynchronized (as in humans and cats) but most sites present high frequency (7-10 Hz) theta waves.

The usual classification of sleep in non-human animals into two stages, REM and NREM, is an oversimplification. In cats (GOTTESMANN et al., 1984) synchronized sleep evolves as a sequence of different phases, which was confirmed and extended for rats (VALLE et al., 1992). In current analysis, the normal sequence of three phases in epileptic rats was reported during synchronized (slow-wave) sleep, which was sometimes followed by an intermediate phase and then by paradoxical (or desynchronized sleep). Synchronized sleep normally starts as S_I, with frequent spindles, followed by S_{II}, in which spindles and delta waves predominate. S_{III}, in which spindles disappear and delta waves are predominant, follows S_{II} (URSIN, 1968). In pre-paradoxical sleep, theta waves occur in the hippocampus but signs of S_I or S_{II} in cortical areas are present. In desynchronized sleep frontal areas are desynchronized (as in humans) but theta waves predominate in all the other sites, either cortical or hippocampal. This sequence was exhibited by healthy and FMUSP-rats alike.

Spike-wave discharges (SWD). These potentials were found in the cortical areas 3 and 10 and in the hippocampal fields, mainly during wakefulness. Most seizures occurred during wakefulness (90.9%), rather more during attentive (63.2%) than in relaxed (27.7%) wakefulness. Seizures were much less frequent during sleep. In synchronized sleep, fits amounted to only 5.8% (2.8% in phase SI and in phase SII, whereas only 0.2% occurred during phase SIII); 1.5% of seizures occurred during the pre-paradoxical phase and 1.8% occurred during the paradoxical phase, as shown in Table 1. An important feature occurs since, in general, the rats return to the same phase of the wakefulness-sleep cycle that was interrupted by the seizure, as Table 1 also shows.

The occurrence of the absence seizures was evaluated by measuring the duration and periodicity of SWD as a function of time. Figure 2A shows a clear-cut burst of SWD during a period of alert wakefulness, interrupting a period of high motor activity, which returns after the SWD has ceased. In Figure 2B, the SWD occurs during a period of relaxed wakefulness. One should note that in the left CA_1 hippocampal field the pathological potentials are present, starting nearly one second before those in the cortical areas 10 and 3. Whereas in Figure 1A motility was entirely interrupted during the absence seizure, rapid clonic movements may be observed in Figure 1B. Figure 3 shows, with a higher degree of resolution, a burst of SWD in cortical and hippocampal sites.

Table 1. Distribution of the prevalence of spike-wave bursts (n=253) along the 24-h period. *Phase*: phase of the wakefulness-sleep cycle during which the seizures occurred. *Before*: phase of the cycle that preceded the seizures. %: percentage of the time of the phase in which the seizures occurred. *After*: phase of the cycle immediately after the seizures. *AW*: attentive wakefulness; *RW*: relaxed wakefulness; *SI*: first phase of synchronized sleep; *SII*: second phase of synchronized sleep; *SIII*: third phase of synchronized sleep; *PP*: pre-paradoxical sleep; *PS*: paradoxical sleep.

Phase	Before	%	After	%
AW	1676	63.2	1696	63.9
RW	734	27.7	733	27.7
SI	75	2.8	125	4.7
SII	74	2.8	52	2.0
SIII	5	0.2	7	0.3
PP	40	1.5	8	0.3
PS	49	1.8	32	1.2
Total	2653	100	2653	100

Behavioral states. The FMUSP-rats showed more behavioral transitions than healthy animals throughout the wakefulness-sleep cycle, as Figure 4 shows. The epileptic rats underwent 302 ± 58 (mean ± s.e.m.) daily changes, i.e., 20.5% above those presented by the normal ones (251.2 ± 63.3), which characterized a significant ($p < 0.02$) difference.

In normal rats, relaxed wakefulness precedes synchronized sleep, which starts as phase S_I and then evolves to S_{II}, S_{III} and desynchronized sleep. In the epileptic rats, however, from attentive wakefulness the animal goes directly to S_{III} or from relaxed wakefulness to pre-paradoxical sleep, but never to paradoxical sleep. In Figure 5, the hypnograms of both epileptic (below) and normal (above) rats are displayed, recording a high overall difference between the two graphs. Fragmentation of the wakefulness-sleep cycle is high in the epileptic animals, as shown in Figure 4.

Duration and incidence of the stages. Wakefulness episodes lasted similarly in epileptic and healthy animals. Incidence of attentive

wakefulness was, however, 19.8% lower (t = -2.20; $p < 0.005$) in the epileptic animals than in the normal group. Relaxed wakefulness incidence was also lower (14.8%) in the epileptic group (t = -3.10; $p < 0.001$).

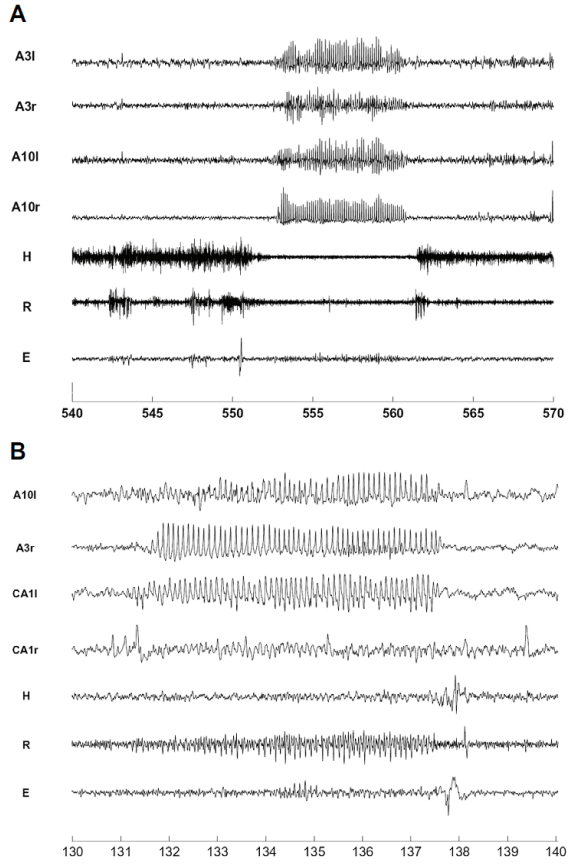

Figure 2. (A) Bilateral burst of spike-wave discharges on area 10 during a period of attentive wakefulness. During the burst the preceding very active head (H), rostrum+vibrissae (R) and eye (E) movements are suppressed, returning after its cessation. $A10_l$: left neocortical area 10. $A10_r$: right neocortical area 10. (B) Burst of spike-wave discharges in left ($A10_l$) and right ($A10_r$) areas 10, in left ($A3_l$) and right ($A3_r$) areas 3 and in the hippocampus during relaxed wakefulness. $CA1_l$, left hippocampal field CA1. $CA1_r$, ibidem, right side. Abscissae: time in seconds after beginning of acquisition by the computer.

Phase S_I occurred significantly less (18.1%; t = -4.24, $p < 0.001$) in the epileptic rats when compared to the normal group, whereas the phase S_{II} incidence was much lower (36.3%; t = -4,08, $p < 0.00001$) and S_{III} tended to increase (9.1%, although not significantly). Pre-paradoxical and paradoxical phases did not undergo significant changes in the epileptic group when compared to normal rats.

Phase S_I of synchronized sleep in the epileptic animals lasted longer (24.4%) than in normal rats (t = 3.22; $p < 0.001$) during daytime. At night, when rats are more active, the mean duration of this stage of synchronized sleep was lower (11%) than in the normal group (t = 2.42. $p < 0.003$). Phase S_{II} also lasted much longer (63.7%) in the epileptic group during daytime (t = 6.33, $p < 0.0001$) and at night (42%, t = 3.54; $p < 0.001$). Phase S_{III} in the epileptic rats was also longer than in the normal group (8.8%, t = -3.37; $p < 0.003$) during daytime but not at night. Paradoxical sleep usually lasted longer in the epileptic rats (13%, t = 2.5; $p < 0.03$), with no significant differences between daytime and nighttime.

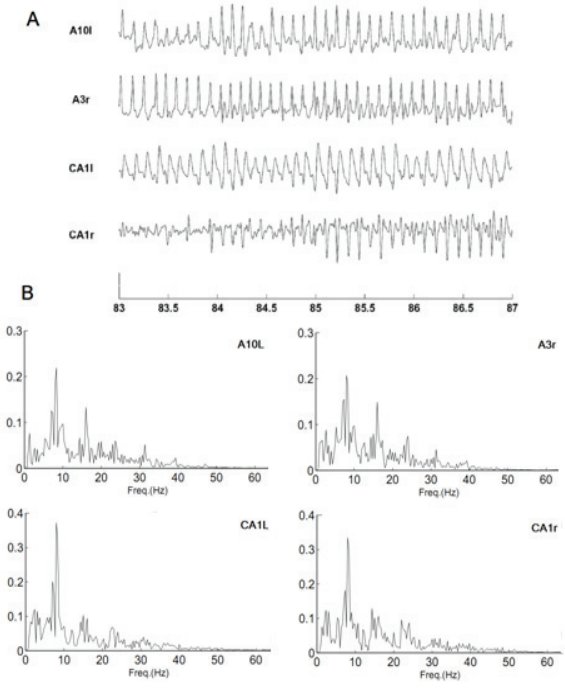

Figure 3. (A) 4-sec sample of a spike-wave burst in the area 10 and in the hippocampus. Notice the conspicuous spike-wave potentials in the hippocampus. (B) Frequency spectra from $A10_l$, $A3_r$, $CA1_l$ and $CA1_r$ respectively. Abbreviations as in Figure 2.

Pre-paradoxical phase did not exhibit any difference among the animals of the two groups. Figure 6 shows the general distribution of the duration of each stage of the wakefulness-sleep cycle. Interestingly, the total duration of the behavioral states in normal and epileptic rats was statistically similar, despite the high fragmentation of the wakefulness-sleep cycle stages, revealing a compensation that is able to keep the total duration within the normal limits.

When a phase of the wakefulness-sleep cycle is interrupted by a SWD, the return to the normal state usually occurs by continuing the interrupted phase, as shown in Figure 2A. Attentive wakefulness may occasionally follow any pre-ictal phase.

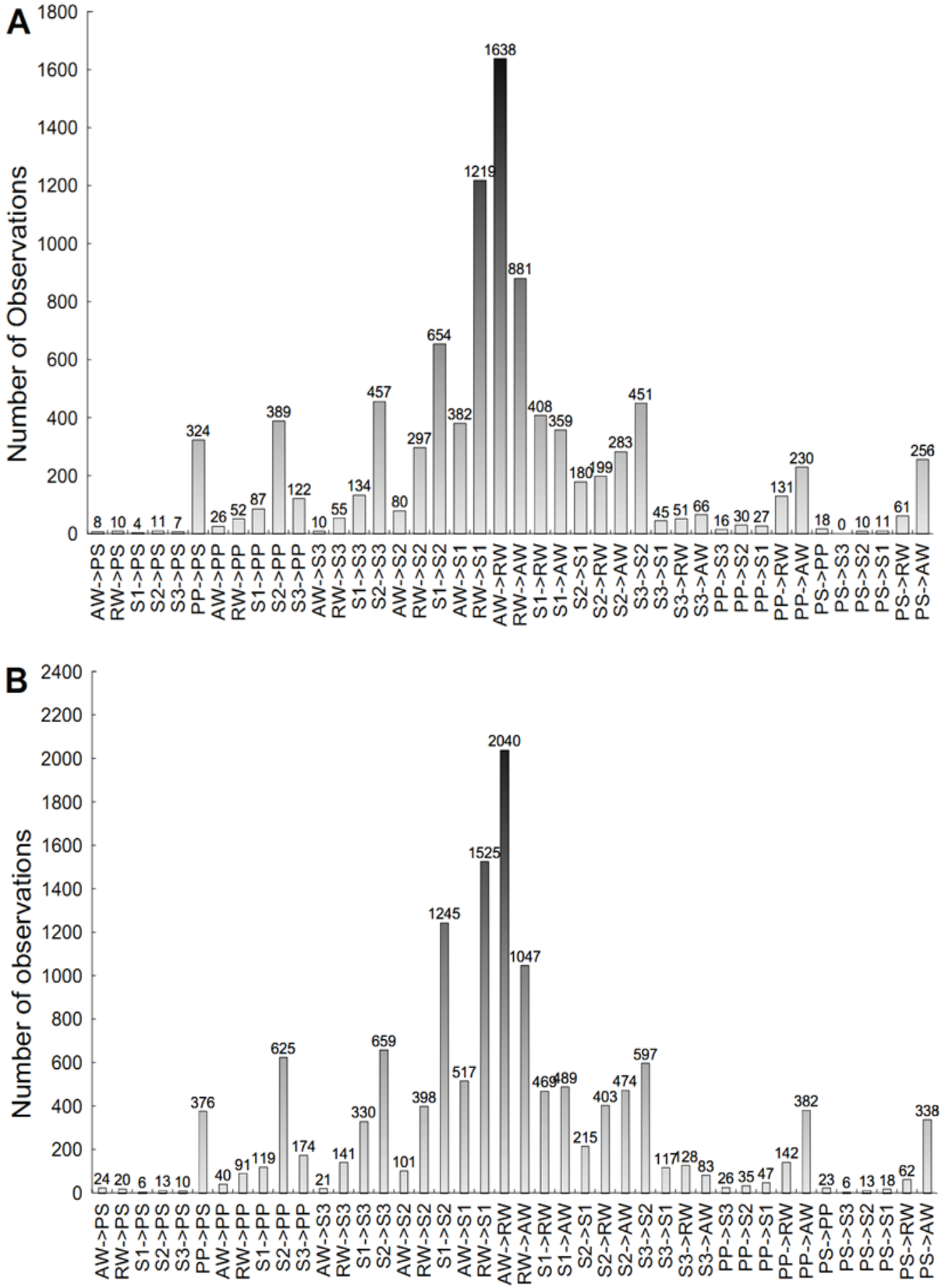

Figure 4. Number of transitions (above the columns) underwent by the wakefulness-sleep cycle in epileptic (A) and normal (B) rats during 24 hours. AW: attentive wakefulness. RW: relaxed wakefulness. SI: phase I of synchronized sleep (spindles). SII: phase II (spindles+delta waves). SIII: phase III (only delta waves). PP: pre-paradoxical sleep. PS: paradoxical sleep.

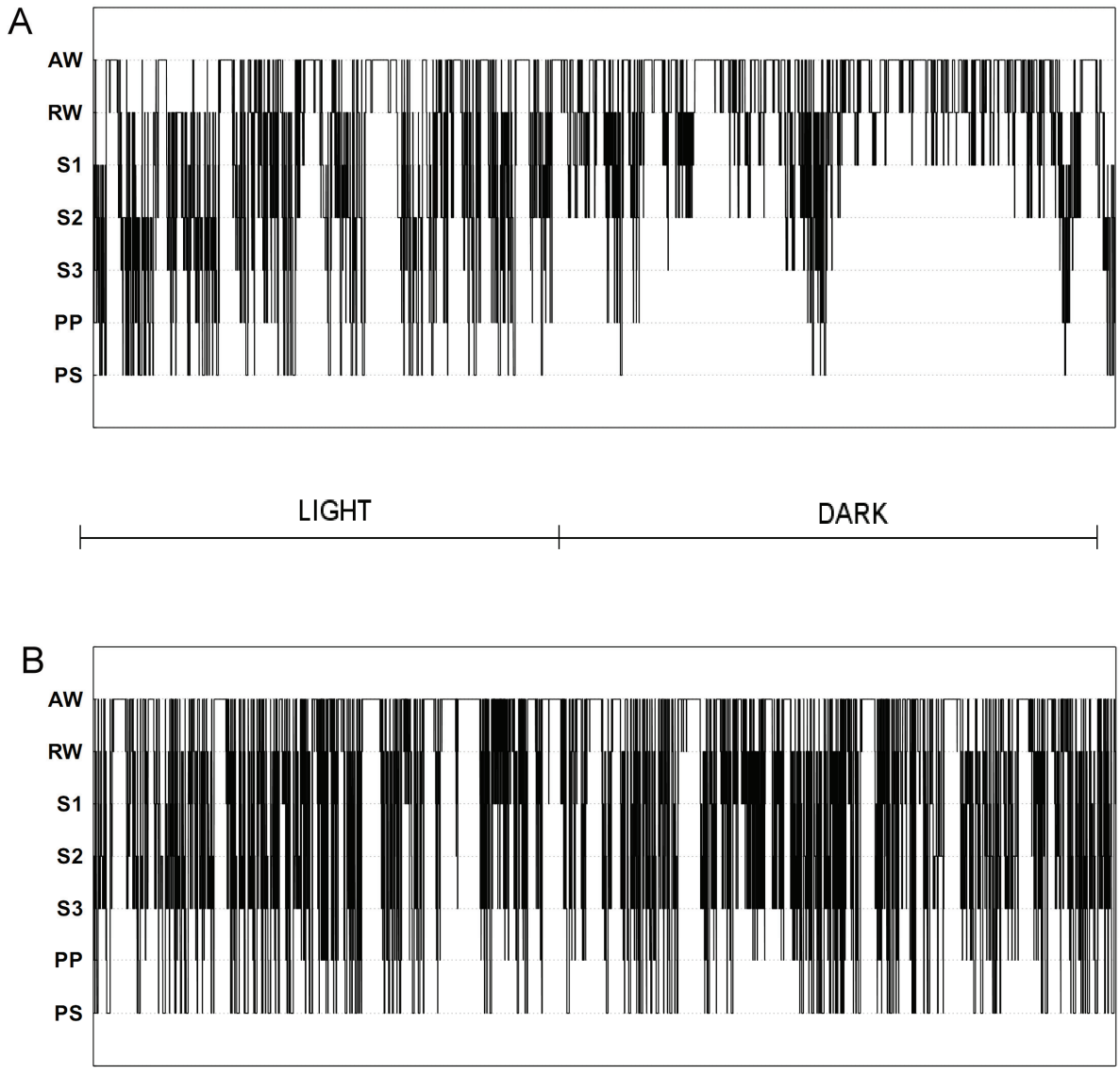

Figure 5. 24-hour hypnograms obtained from a healthy (A) and an epileptic (B) rat. Observe the great fluctuation of the different phases of sleep during the night period as well as the great fragmentation throughout the whole cycle. AW, RW, SI, SII, SIII, PP, PS: as in Figure 4.

Discussion

FMUSP-rats present iterative spike-wave discharges in neocortical areas, as has been reported in other rodent experimental models of absence-like seizures (VERGNES et al., 1982; VAN LUIJTELAAR; COENEN, 1986; SERIKAWA et al., 1987). However, departing from all other models, with the probable exception of the stargazer mutant mouse (COENEN et al., 1992), the spike wave discharges (SWD) in the rats under analysis occur regularly also in the hippocampus (ANDRÉ et al., 2014). The lack of spike-wave complexes in the hippocampus during absence seizures in rodents has been almost imposed as a sign of this kind of epilepsy (MARESCAUX et al., 1992; BAL, McCORMICK, 1996; McCORMICK, CONTRERAS, 2001), but SWD in the hippocampus of FMUSP rats are clearly present (ANDRÉ et al., 2014).

The absence seizures in FMUSP rats occur predominantly during attentive wakefulness, as observed in humans (HALÀSZ, 1972; 1981; MONTPLAISIR et al., 1985) and in GAERS rats (PINAULT et al., 2006), which probably accounts, at least partially, for a 19.8% reduction of the mean incidence in wakefulness. When a seizure ceases, the return is generally to the pre-ictal phase; otherwise, return occurs mostly at phase S_I of synchronized sleep. The same pattern prevails when the seizure interrupts any synchronized sleep phase. If the

seizure takes place during paradoxical sleep, the cycle returns mostly to attentive wakefulness, which may be related to the fact that when a paradoxical phase ends in normal rats, it is frequently ensued by a short period (1-2 sec) of attentive wakefulness. Apparently, there is a trend for the animal to stay awake after an absence seizure or to evolve to an early phase of synchronized sleep, S_I, which occurs next to wakefulness in incidence.

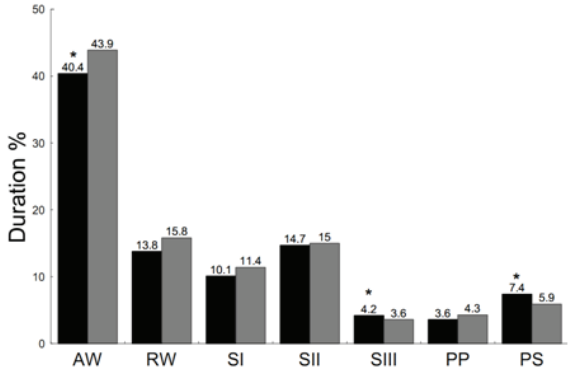

Figure 6. Graphic Representation of the relative durations of each phase of the sleep-wakefulness cycle during 24 hours of registration. AW, RW, SI, SII, SIII, PP, PS: as in figure 3. Black columns: epileptic rats. Gray columns: normal rats.(*) Significant statistical differences from control ($p < 0.05$).

According to the type of epilepsy, sleep may precipitate or at least facilitate the onset of epileptic seizures. Partial seizures tend to occur more often during states of arousal, whereas generalized seizures are more frequent during states of relaxed wakefulness or synchronized sleep (FUTATSUGI; RIVIELLO JR., 1998; QUIGG, 2000; URE, PERASSOLO, 2000). On the other hand, paradoxical sleep is a potent blocker of epileptic seizures (DECLERCK, 1986; PELED, LAVIE, 1986; MALLOW, 1996; HELLIER; DUDEK, 1999; AVANZINI; PANZICA, 2000) or its deprivation reduces SWD incidence similar to WAG/Rij rats (PEETERS et al., 1989). However, a few seizures were detected in FMUSP rats during paradoxical sleep. This fact was unexpected since SWD are characteristically a sign of absence and during paradoxical sleep oneiric behavior in rats is very intense (URSIN, 1968). To the best of our knowledge, the occurrence of SWD during paradoxical sleep has never been reported in humans, probably because it has never been or was poorly investigated. It would be extremely important to find out such an occurrence because humans may tell their dreams and an influence of the seizure on the dream content and flow could be identified (NG; PAVLOVA, 2013).

Epilepsy is well known to disrupt acutely and chronically the organization and microstructure of sleep (MALLOW; VARMA, 1995; QUIGG, 2000). Acutely, a seizure in humans obviously breaks primarily the normal flow of the sleep-wakefulness cycle and secondarily may disrupt the sleep organization (MONTPLAISIR et al., 1985; GANDOLFO et al., 1990; MALLOW, 1996). *Status epilepticus* due to domoic acid administration has suppress the occurrence of sleep in rats, which reappears two days after cessation of the seizure and the normal cycling of wakefulness-sleep is fully recovered only four days after the seizures (DAKSHINAMURTI et al., 1991).

WAG/Rij rats, which are a model of absence seizures, show sleep-wakefulness changes although wakefulness is little affected. However, the order of the sleep cycles is altered (DRINKENBURG et al., 1995; KUZNETSOVA et al., 1996) and pre-paradoxical phase does not have a longer duration than in normal rats, differing from what occurred in FMUSP rats where this phase was not affected.

Faradji et al. (2000) found that GAERS rats exhibit stable amounts of wake state and slow wave sleep, distributed through clear circadian rhythms, analogous to those of Wistar non-epileptic animals, with a quantitative deficit in PS.

Fragmentation, the main change in the sleep-wakefulness cycle in FMUSP rats, is highly influenced by changes in the duration of its phases. Although phase S_I, phase S_{II} and phase S_{III} lasted much longer in the epileptic rats than in the normal group during daytime, there was a surprising difference among them at night: whereas S_I duration decreased at night, S_{II} increased much less in the period, and S_{III} increased in daytime but did not change at night. In fact, p re-paradoxical and paradoxical sleep did not change significantly. Such differences are suggestive of an independent generation of each phase of the cycle, inasmuch as the change of one does not seem to be unequivocally correlated with the change of the others. If one single process were involved in the generation of all the phases, it should be expected that similar alterations would occur in all of them.

The incidence of each phase was significantly reduced, except S_{III} of synchronized sleep and paradoxical sleep, which accounts for the fact that the total duration of the behavioral states in both normal and epileptic rats was statistically similar, despite the high fragmentation of the wakefulness-sleep cycle stages observed in the epileptic rats. This apparently reveals a compensation that keeps total duration within normal limits. Compensation could be identified because the duration and incidence of

the cycle's phases were studied independently from the interruption of the phases. Therefore, the fragmentation of the cycle seems to be due to an impairment of the processes that maintain sleep and wakefulness. Intrinsic and systemic pathologic changes of the brain are probably affecting not only sleep and wakefulness in FMUSP rats but probably other functions too. Since seizures may arise from different brain rhythms/behavioral states, we still do not know whether there is only one neuronal mechanism underlying seizure initiation or whether there is a set of principles that explains why similar seizures arise from differing sleep–wake states? The above results seem to add new information that hopefully helps one understand the mechanisms underlying sleep and epilepsy interactions in this particular rat model. Deeper knowledge, prediction and treatment of human epilepsy may be derived from this kind of investigation.

Conclusion

The electrophysiological and behavioral characteristics of FMUSP-rats call for an accurate and long-range analysis, because of its resembling the absence-like human seizures but also because of some discrepancies in comparison with other genetic and experimental epilepsy models described so far.

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