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Changes in cortical and hippocampal EEG activity accompanying spontaneous electrocortical seizures in rats

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Abstract. The purpose of the present study was to find out whether the occurrence of bursts of spontaneous spike-wave discharges (SWD) in rat neocortex is related to a particular state of vigilance (level of arousal), as some authors suggested, or rather to transitions from one state to another as postulated by others. Patterns of cortical and hippocampal EEG preceding and following the SWD bursts were studied in rats. It has been found that the beginning of an SWD episode is usually preceded by a shift of cortical activity toward synchronization and replacement of the rhythmic slow activity (RSA) in the hippocampus by large irregular activity (LIA). After SWD, the cortical activity is usually more desynchronized and RSA is present more frequently than just before its onset. An analysis of selected episode-free and episode-rich EEG segments revealed that SWD's occur in abundance at the periods characterized by frequent changes of the hippocampal EEG pattern but are absent during the periods in which long-lasting RSA trains dominate in the record. Thus, the data confirm that SWD occurrence is related more to transitions from one state to another than to a particular state as such. They also indicate that the preferable conditions for SWD's appear when arousal is decreasing from a moderate to a lower level.

Key words: EEG, cortex, hippocampus, spike-wave discharges, arousal

INTRODUCTION

In many inbred as well as outbred rat strains, a certain proportion of subjects show spontaneous, nonconvulsive generalized cortical EEG seizures in the form of bursts of 7 - 10 Hz spike-wave discharges (SWD), resembling those seen in human absence epilepsy (see Coenen et al. 1992, Marescaux et al. 1992). The bursts start to appear when the rat is about 3 months old and the rate of their occurrence as well as their duration increase with age (Aldinio et al. 1985, Aporti et al. 1986, Vergnes et al. 1986). Some authors regard rats with SWD-s as an animal model of human absence epilepsy and use them for the evaluation of the proconvulsive or anticonvulsive potency of drugs (eg. Peeters et al. 1988). According to others, the increase in the SWD activity with age reflects the progress in the age-related neurodegeneration of the forebrain cholinergic system (Aldinio et al. 1985, Buzsaki et al. 1988, Gage et al. 1988). It justifies the use of the SWD measurement in testing drugs for their efficacy in the treatment of senile and presenile dementias (Aldinio et al. 1985, Aporti et al. 1986, Riekkinen et al. 1991). There is a growing suspicion that exposure to some industrial and environmental neurotoxins may contribute to age-related neurodegenerative processes (Weiss 1991, Reuhl 1992). SWD measurement may thus appear a useful tool in detecting such effects.

The main obstacle in applying SWD measurement for an assessment of the effects of drugs or xenobiotics is the natural, very high variability of SWD occurrence. Recognition of the factors underlying this variability may allow their control. Relevant data suggest that SWD occurrence is related to the level of behavioural and electroencephalographic arousal. The nature of this relationship, however, is not clear. According to Vergnes et al. (1982, 1986) and Buzsaki et al. (1988), SWD episodes occur preferably during a state termed "awake immobility" and are absent during other states (i.e. during voluntary movements and during sleep). Recent investigations by Drinkenburg et al. (1991) suggest, however, that SWD bursts occur most frequently on transitions from one state to another (namely from light slow-wave sleep to wakefulness). In our previous studies (Gralewicz et al. 1994) we found a positive correlation between the number of SWD episodes and the cumulative duration of a state classified as "moderate arousal", (MA - an equivalent of the "awake immobility"), which seemed to confirm the observations of Vergnes et al. (1982, 1986) and Buzsaki et al. (1988). However, the correlation was evident in each single session but not when the corresponding hours of three successive sessions were compared. In fact, it appeared that in the first hour of the second and the third session the number of SWD episodes was significantly increased but the amount of MA decreased as compared with the corresponding hour of the first session. The distribution of other states (HA (high arousal), LA (low arousal), SWS (slow wave sleep) and PS (paradoxical sleep)) indicated more frequent shifts in arousal during early periods of the second and third session. This might confirm, albeit indirectly, the validity of Drinkenburg et al. (1991) observations. Therefore, the main purpose of the present studies was to elucidate whether the spontaneous SWD bursts occur preferably during a certain state or rather when a change in state is in progress. Secondly, we tried to find out a relationship between the number of state changes and the number of SWD episodes in a given animal.

Drinkenburg et al. (1991) estimated changes in arousal (level of vigilance) around the SWD episodes by comparing mean spectrograms of 5 s epochs of the neocortical EEG immediately preceding and following each episode. Large changes may occur in the EEG morphology during five seconds and the result of the analysis of such a long epoch may not be informative enough. Therefore, in the present studies two shorter (2 s) fragments of EEG before and after each SWD burst were subject to the analysis. Apart from the neocortical, also the hippocampal EEG was analysed. It was justified by the strong relation of the hippocampal EEG morphology to the behavioural state (Vanderwolf 1988). Moreover, the fact that the SWD activity does not propagate to the limbic structures (Vergnes et al.

1989) allows one to study changes in arousal not only before and after but also during the SWD episodes.

METHODS

Material

In the present studies, the material (EEG recordings) collected during previous experiments was used. The selected seven recordings were obtained from seven rats (8-month-old males of IMP-DaK outbred stock) characterized by the highest rate of SWD occurrence. Each recording comprised a period not shorter than three consecutive hours. The EEG activity was recorded from the frontoparietal cortex (bipolar depth-to-surface derivations) and dorsal hippocampus (bipolar derivations).

Analysis of the recordings

Four seconds fragments of cortical and hippocampal EEG directly preceding and following each SWD episode were analysed visually. Each of the 4 s fragments was additionally divided into two 2 s sections. The sections covering 4 s preceding the SWD were denoted as 4-2 s and 2-0 s periods and those referring to 4 s after the SWD were denoted as 0-2 s and 2-4 s periods. The type of hippocampal activity was also determined in the first two seconds after the onset of the episode (start) and in the last two seconds of its duration (end). Cortical activity was classified as desynchronized, partially synchronized or synchronized. In the case of the hippocampal EEG the analysis consisted in determining what type of activity - rhythmic slow activity (RSA or theta rhythm) or large irregular activity (LIA) - dominated during the distinguished periods (Fig. 1).

In order to find out a possible relationship between the occurrence of SWD episodes and the stability of the electroencephalographic arousal, the number of changes (shifts) in the EEG morphology was counted in four (out of seven) recordings with the highest SWD rate. Transitions from RSA to LIA are more readable in the hippocampal EEG then in the cortex and they are usually accompanied by cortical transitions. Therefore, the shifts were determined only from the hippocampal EEG. The shifts from RSA to LIA, and vice versa, were counted and the selected records were divided into sections (blocks), each containing 100 shifts. In each block, the number of SWD episodes, the cumulative duration of SWD activity, and the ratio between the number of shifts and the number of SWD episodes were calculated.

In some recordings SWD episodes were encountered in groups; the periods with no episodes and those with numerous episodes appeared alternately. In order to find out the differences between the "favourable" and "unfavourable" conditions for

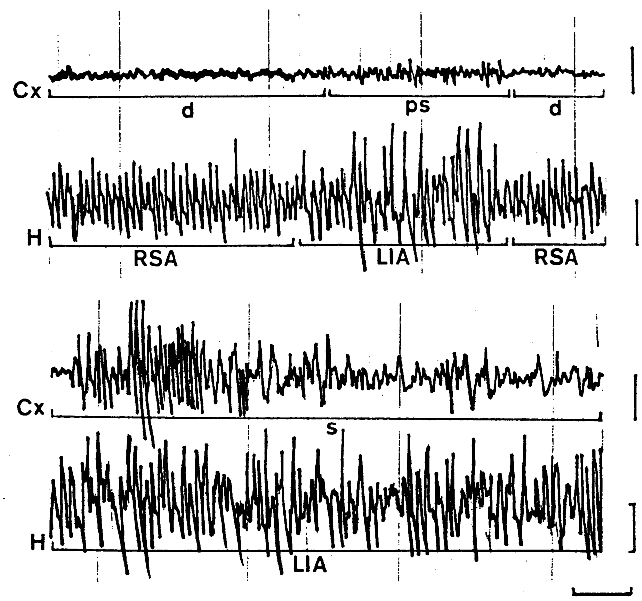

Fig. 1. Two fragments of a record illustrating the types of cortical and hippocampal activity distinguished in the course of the visual analysis. Cx, cortical EEG (frontoparietal cortex, bipolar depth-to-surface derivations); H, hippocampal EEG (dorsal hippocampus, bipolar derivations). Underlined types of cortical activity: d, desynchronized; ps, partially synchronized; s, synchronized (slow wave sleep with spindles). Underlined types of hippocampal activity: RSA, rhythmic slow activity (theta rhythm); LIA, large irregular activity. Animal state while the upper record has been made: awake, sitting quietly, occasional slight orienting movements of the head. Animal state when the lower record has been made: lying immobile with head burried in sawdust. Calibrations: horizontal, 1 s; vertical, 200 μV.

SWD occurrence, episode-free and episode-rich fragments of a continuous EEG, covering periods not shorter than 2 min, were selected. Each fragment was divided into sections according to the number of shifts in the hippocampal EEG morphology. The cumulative episode-free and episode-rich periods were compared with respect to the percentage of sections classified according to the type of hippocampal activity and the duration of the section.

RESULTS

Changes in the cortical and hippocampal EEG preceding and following SWD episodes

Seven 3 h records from seven animals were analysed. 426 SWD episodes were detected in these records. The data illustrating changes in the cortical and hippocampal EEG accompanying SWD episodes are presented in Tables I and II. Friedman two-way ANOVA (Siegel 1956), applied to compare the prevalence of the distinguished types of cortical activity (expressed as percent of the total number of SWD episodes in each recording) in the consecutive 2 s periods before and after the SWD episodes, revealed significant differences in the case of desynchronization (X^2=12.04, *df*=3, *P*<0.01), no differences for partial synchronization, and significant differences for synchronization (X^2=13.07, *df*=3, *P*<0.01). The prevalence of desynchronization was significantly lower in the 2-0 s period than in the 4-2 s (*P*<0.02), 0-2 s *P*<0.05), and 2-4 s (*P*<0.02) periods (Wilcoxon test). The prevalence of synchronization was significantly higher in the 2-0 s period as compared with both the periods after SWD (*P*<0.02 in both cases) but not with the 4-2 s period (see Table I). When the prevalence of synchronization and desynchronization was combined, the result of the analysis was reciprocal to that in the case of desynchronization, i.e. in the 2-0 s period the cortex was in a state of decreased activity much more frequently than in the remaining periods. The picture encountered most frequently was as follows. Before the onset of an SWD episode there is a more or less evident increase in the amplitude and decrease in the frequency of the cortical activity. The discharges "emerge" from the background EEG attaining their maximum amplitude after a few cycles. Toward the end of the SWD episode the amplitude of discharges decreases but their frequency increases. The seizure stops abruptly and the cortical EEG assumes the low-amplitude desynchronized pattern (Fig. 2)

The changes in the hippocampal EEG were more visible (Table II). The comparison of the distinguished 2 s periods by Friedman ANOVA revealed significant differences with respect to the RSA prevalence (X^2= 20.92, *df*=5, *P*<0.001). In the 4-2 s

TABLE I

Cortical activity before and after SWD episodes (in percent of the episode numbers)

Type of cortical activity		Before SWD		After SWD		Friedman ANOVA	
		4-2 s	2-4 s	0-2 s	2-4 s	chi-sq	*P*
Desynchronization	mean	60.3	30.0	63.9	71.2	12.04	<0.01
	SE	8.5	5.5	6.7	6.8		
Partial synchronization	mean	31.5	54.8	32.5	26.3	6.94	NS
	SE	6.7	5.9	6.1	6.2		
Synchronization	mean	8.2	15.6	3.7	2.5	13.07	<0.01
	SE	2.8	15.3	1.5	1.3		

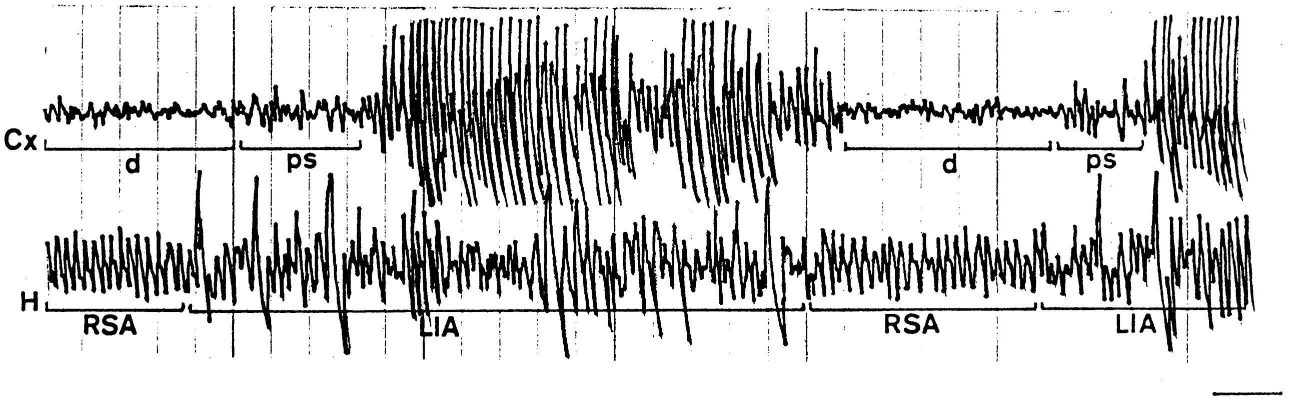

Fig. 2. Fragment of an EEG recording illustrating the frequently encountered pattern of changes in the cortical and hippocampal activity accompanying SWD episodes. Description of the records and calibrations as in Fig. 1.

period RSA was present in almost 50% of cases but only in 12% in the 2-0 s period ($P<0.05$, as compared with the periods of 4-2 s, 0-2 s and 2-4 s) and in 8.8% in the first two seconds of SWD episode duration ($P<0.05$, as compared with all the remaining periods except the 2-0 s period). No other differences were found. Typically, the changes in the hippocampal activity accompanying SWD episodes proceed as follows: RSA, if present, is replaced by LIA before the beginning of SWD's and the latter activity persists during most of the episode duration. RSA may reappear at the end of the episode or soon afterwards.

At the end of this analysis we compared the electroencephalographic arousal in the 2-0 s and 0-2 s periods. The arousal level was classified on the basis of hippocampal and cortical EEG as high (HA), moderate (MA) or low (LA), according to the criteria adopted earlier (Gralewicz et al. 1994). It has appeared that the state encountered most frequently at the onset of SWD episodes was MA (in 72.2% of cases), the next was HA (15.5% of cases) and LA (11.4% of cases). The joint contribution of SWS and PS was negligible. After SWD episodes the proportion of MA and LA fell to 54.0% and 4.8%, respectively, but that of HA increased to 40.2% (Table III).

Relationship between the incidence of SWD episodes and the stability of electroencephalographic arousal

The data from this part of the analysis are presented in Table IV. The differences in duration of the blocks (i.e. sections with 100 shifts from RSA to LIA in the hippocampal EEG) from the same as well as from different recordings were rather negligible. The recordings did not vary a lot with respect to the mean number of SWD episodes per block and the mean SWD duration. However, the differences between successive blocks of the same recordings with respect to the SWD number, cumulative dura-

TABLE II

RSA occurrence before, during and after SWD episodes (in percent of the episode numbers)

	Before SWD		During SWD		After SWD		Friedman ANOVA	
	4-2 s	2-0 s	start	end	0-2 s	2-4 s	chi-sq	*P*
Mean	49.1	12.7	8.8	31.2	34.4	46.0	20.92	<0.001
SE	7.5	2.7	3.5	6.8	4.8	6.7		

TABLE III

Distribution of states around SWD episodes (in percent of the total number of episodes). Legend: HA, high arousal (cortical activity desynchronized, hippocampal activity - RSA; MA, moderate arousal (cortical activity desynchronized or partially synchronized, hippocampal activity - LIA); LA, low arousal (cortical activity synchronized, hippocampal activity - LIA, for a period no longer than 10 s); SWS, slow wave sleep (cortical activity synchronized, hippocampal activity - LIA, for a period longer than 10 s); PS, paradoxical sleep (cortical and hippocampal activity as during HA but the rat is lying immobile)

Before / After	HA	MA	LA	SWS	PS	Σ
HA	4.6	10.7	0.2	0.0	0.0	15.5
MA	33.3	36.8	2.2	0.0	0.0	72.2
LA	2.2	6.8	2.4	0.0	0.0	11.4
SWS	0.2	0.5	0.0	0.0	0.0	0.7
PS	0.0	0.0	0.0	0.0	0.2	0.2
Σ	40.2	54.8	4.8	0.0	0.2	100.0

tion of SWD activity, and to the ratio: number of shifts/number of SWD episodes were surprisingly high.

Favourable and unfavourable conditions for SWD occurrence

Four SWD-rich and five SWD-free fragments (blocks) were selected from one of the seven recordings. The sections which could be classified as SWS or PS were not present in any of the selected blocks. The cumulative duration of the SWD-rich period was 904 s, the number of shifts in the hippocampal EEG - 147 (the mean between-shift interval - 6.19 s), and the total number of SWD episodes was 33. The cumulative duration of the SWD-free peri-

TABLE IV

Relationship between the SWD occurrence and the number of shifts in the hippocampal activity. (Each block contains 100 shifts)

No. of rat and number of blocks		Block duration (in s)	Number of SWD episodes per block	Total duration of SWD episodes	Number of shifts/number of SWD episodes ratio
6	mean	1130	10.8	51.2	11.0
n=5	range	(888-1342)	(6-20)	(25-112)	(6-16.7)
	median	1230	8	30	12.5
8	mean	1318	16.2	115.2	9.3
n=5	range	(1025-1749)	(6-26)	(28-186.5)	(3.8-16.7)
	median	1117	20	143	5.0
19	mean	1098	12.4	47.1	8.6
n=5	range	(810-1440)	(8-17)	(36-68.5)	(5.9-12.5)
	median	1170	11	44	9.1
3	mean	925	9.8	58.1	12.0
n=5	range	(879-945.5)	(6-16)	(34.5-96)	(6.2-16.7)
	median	936	8	43	12.5

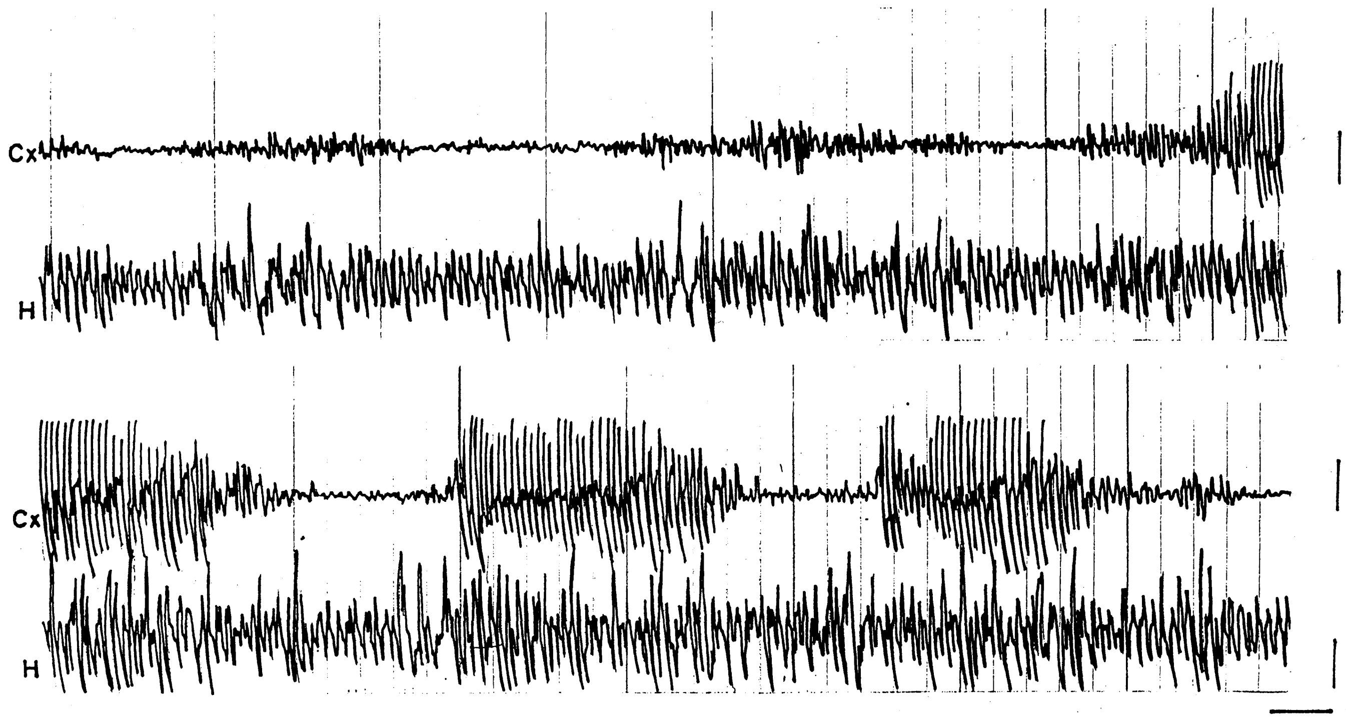

Fig. 3. Fragment of an EEG recording from the SWD-rich period. Description of the records and calibrations as in Fig. 1. Note the similarity of the changes in the hippocampal EEG accompanying SWD episodes and the periodic increases of the cortical EEG amplitude.

od was 2632 s, the number of shifts - 182 i.e. the mean between-shift interval was 14.5 s. Table V presents the percentage distribution of the EEG sections distinguished according to the duration and the type of hippocampal activity (RSA or LIA). As it can be seen, the proportion of sections with RSA

TABLE V

Percentage distribution of sections of the hippocampal record within the episode-rich and episode-free periods, classified according to their duration and the type of hippocampal activity

Type of hippocampal activity		Percentage distribution of sections											
		Episode-rich periods Section duration in seconds						Episode-free periods Section duration in seconds					
		1-5	6-10	11-20	21-40	40-∞	Σ	1-5	6-10	11-20	21-40	40-∞	—
LIA	%n	24.6	19.1	12.3	0.7	0.0	56.7	19.4	14.4	14.4	4.9	1.0	54.1
	%t	14.5	23.3	30.8	2.8	0.0	71.4	4.2	4.5	15.3	9.5	8.1	41.6
RSA	%n	33.5	7.5	1.4	0.0	0.0	42.4	27.6	7.2	5.5	1.0	3.9	45.2
	%t	16.8	9.1	2.6	0.0	0.0	28.5	5.6	4.2	5.5	2.0	40.8	58.1
	Σ%n	58.1	26.6	13.7	0.7	0.0	99.1	47.0	21.6	19.9	5.9	4.9	99.3
	Σ%t	31.3	32.4	33.4	2.8	0.0	99.9	9.8	8.7	20.8	11.5	48.9	58.1

and LIA is similar in SWD-rich and SWD-free period. In both the periods short sections (1-5 s and 6-10 s) constituted a majority of the total number of sections (84.7% and 68.6%, respectively). In the SWD-rich period, however, their cumulative duration amounted to 63.7% of the total time, but only to 18.5% in the case of the SWD-free period. The long sections (21-40 s and above) were present practically only in the SWD-free period and although not numerous (10.8% of the total number) they comprised 60.4% of the cumulative duration of this period. As to the type of hippocampal activity, the proportion of sections with RSA and LIA was similar in both the SWD-rich and SWD-free period. However, the sections with LIA contributed more to the cumulative duration of the SWD-rich period than the sections with RSA (71.4% and 28.5%, respectively), whereas a reverse relationship was found in the case of the SWD-free period (sections with LIA - 41.6%, sections with RSA - 58.1%). Moreover, among the long sections (21-40 s and above) which contributed most to the total duration of the SWD-free period, the sections with RSA prevailed (Table V).

DISCUSSION

The results of the present studies confirm, in general, the Drinkenburg et al. (1991) observations that the SWD episodes occur preferably when the level of arousal changes. Comparing mean spectrograms of 5 s epochs of cortical activity preceding and following the SWD episodes, the above authors found that 57.7% of SWD bursts occurred on transitions and that most of these transitions were from light slow sleep (an equivalent of LA in our studies) to passive awake (MA according to our classification).

If only the 2 s EEG sections neighbouring the SWD episodes were taken into account, our results might be regarded as fully concordant with those of Drinkenburg et al., i.e. they confirm that the animal is usually more aroused after the SWD episode than before. They do not confirm, however, the supposition that the optimum conditions for SWD occurrence are met when arousal increases. In fact, the comparison of the EEG morphology during two successive 2 s sections preceding each SWD episode suggests that the episode begins when arousal decreases. Accordingly, what Drinkenburg et al. (1991) regarded as the change accompanying SWD occurrence might have been, in fact, the change accompanying its extinction, i.e. the discharges stopped when the arousal level increased. Whether SWD's play an active role in this increase, (as suggested by Drinkenburg et al. 1991) remains to be seen. In the present studies, RSA was encountered more frequently at the SWD episode offset than at the start. In most of the cases, however, the same type of hippocampal activity, i.e LIA, was present in these two periods. Therefore, no firm conclusion concerning the direction of change in arousal during SWD episodes could be drawn.

The findings of our study, confirming and supplementing those of Drinkenburg et al. (1991), seem to support the assumption that the number of SWD episodes and the number of shifts in the arousal level might remain in relatively stable proportions in a given animal. This expected stability has not been found (see Table III). However, as the comparison of the episode-free and episode-rich periods has shown, SWD episodes occur in abundance when the hippocampal record is composed mainly of short sections of RSA and LIA but are absent when long trains of RSA dominate in the hippocampal EEG. It may mean that it is not the absolute number of shifts but the rate at which they follow each other that may significantly influence the SWD occurrence.

According to Drinkenburg et al. (1991), the fact that spike-wave discharges do not occur when the electroencephalographic arousal is either high (as during the locomotor activity and paradoxical sleep) or very low (as during the slow wave sleep) suggests that the optimum level of arousal for SWD's lies somewhere between these two extremes. While analysing recordings from the episode-rich periods, one may have an impression that SWD bursts substitute in part the transient slowings and increases in the amplitude of the cortical EEG (see Fig. 3). If one regards the above changes as an evidence of transient falls of arousal, then the moment when the burst starts may thus denote the point in time at which the level of arousal falls to the suggested optimum level and the cessation of the burst may indicate the moment when the arousal rises again to a level unfavourable for SWD's. It is worth noting, however, that the suggested optimum may also be reached when arousal increases from a low, SWD-unfavourable level, as on awakenings, and that the discharges may stop not only when the arousal increases after a transient decrease but also when the decrease proceeds. In fact, all of these combinations were encountered in Drinkenburg et al. (1991) as well as in our records (see Table IV). In the Drinkenburg et al. (1991) studies, however, the most frequently encountered state before SWD was the light and deep slow wave sleep It might be due to the high contribution of these states in their 24 h recordings. Therefore, a high proportion of the fluctuations which give rise to the optimum conditions for SWD, were transient increases of arousal from the dominating low level. In our rats the awake states (HA, MA and LA) were prevailing during the 3 h recording. Hence, the majority of these fluctuations on which SWD episodes could occur were transient decreases of arousal. Awake states were probably dominant also in the experiments of other authors relating SWD episodes with the state of awake immobility (see Vergnes et al. 1982, 1986, Aporti et al. 1986).

Summing up, the present data confirm that the optimum conditions for SWD's appear in the periods characterized by frequent changes in the morphology of cortical and hippocampal EEG implying fluctuations of arousal level. According to some authors, the periods characterized by unstable EEG may be regarded as transitional states (Depoortere et al. 1991, Drinkenburg et al. 1991). If SWD is to be used as an index of the effect of drugs or other factors, the presence and duration of such states should be carefully observed. In order to distinguish such states in our material, a change of the criterion of the HA state, i.e. imposing 10 s, instead of 2 s, as the minimum duration of the sections with RSA in the hippocampus and desynchronization in the cortex, might suffice. Then, after subtracting the cumulative duration of SWS, PS and HA from the total duration of the analysed recording, what remains will be the sought after "transitional state".

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