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Spike-wave discharges and sleep spindles in rats

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Abstract. Sleep spindles and spike-wave discharges are thought to originate from the same thalamic pacemaker. In the present work it is investigated whether sleep spindles and spike-wave discharges are also sensitive for the same drugs. Adult male WAG/Rij rats were chronically implanted with frontal and occipital EEG electrode pairs. Rats were intraperitoneally injected with clonidine (0.00625 mg/kg), phenobarbital (20 mg/kg), flunitrazepam (0.188 mg/kg). Frontal and occipital sleep spindles and mainly frontal spike-wave discharges were seen in the electroencephalogram. Phenobarbital and flunitrazepam reduced the number of spike-wave discharges and enhanced frontal sleep spindles, while clonidine facilitated spike-wave discharges and reduced frontal sleep spindles. The results of these three drugs indicate a reciprocal relationship between the number of frontal sleep spindles and the number of spike-wave discharges. Only clonidine facilitated occipital sleep spindles without an effect on spike-wave discharges. It can be concluded that frontal and occipital sleep spindles have a different pharmacological profile. Futhermore, the inverse relationship between frontal sleep spindles and spike-wave discharges may suggest that sleep spindles and spike-wave discharges are controlled by a single controlling system. However, in order to explain the clonidine data on occipital sleep spindles another factor must be incorporated in properties of the mechanism(s) involved in EEG oscillations.

Key words: sleep spindles, spike-wave discharges, thalamic pacemaker, rats, electroencephalography, barbiturates, benzodiazepines, a2-agonist clonidine

INTRODUCTION

The interest in the pacemaker involved in the generation of sleep spindles has increased abundantly since the work of mainly Steriade, Llinás, McCormick and colaborators (Steriade and Llinás 1988, Steriade et al. 1993, von Krosigk et al. 1993, Steriade et al. 1994). These authors have described extensively properties of thalamic relay cells and their interactions with neurons from the reticular thalamic nucleus in *vivo* and *in vitro*. It is suggested in their work that sleep spindles and spike-wave discharges are originating from the same thalamic pacemaker and that self-sustained afterdischarges may develop in a further synchronization process towards the characteristic for absence epilepsy, spike-wave discharges. Also others have studied the relationship between spike-wave discharges and sleep spindles. Gloor and colleagues (Gloor 1979, Gloor et al. 1979, Kostopoulos and Gloor 1982, Gloor and Fariello 1988, Gloor 1995) have demonstrated in the feline penicillin model that spike-wave discharges have their origin in thalamic sleep spindles. Thalamic spindles are transferred to cortical neurons through the axons of relay neurons and transformed into spike-wave discharges when the cortex is in a hyperexcitable state.

Almost all above mentioned work has been done in cats, few papers have explicitly aimed their research efforts towards the relation between sleep spindles and spike-wave discharges in other species, such as in rats. A complicating factor is the existence of two types of sleep spindles in rats: Terrier and Gottesmann (1978) and Gandolfo et al. (1985) showed the existence of frontal and occipital spindles. It is of interest that also in humans two (anterior and posterior) types of sleep spindles have been described (Gibbs and Gibbs 1950, Jankel and Niedermeyer 1985, Scheuler 1990-1991, Jobert et al. 1992). This raises the question whether spike-wave discharges are indeed related to frontal sleep spindles and if so, what is the role of the occipital sleep spindles?

Rats of the WAG/Rij strain spontaneously show, next to sleep spindles, also hundreds trains of spike-wave discharges per day and these spike-wave have a pharmacological profile similar to absence epilepsy in man (Peeters et al. 1988). Therefore these rats are considered as a valid model for generalized absence epilepsy (van Luijtelaar and Coenen 1986, 1989, Coenen et al. 1991). The WAG/Rij model is very close to Vergnes and Marescaux GAERS model (e.g. Marescaux et al. 1984) and the morphology of the spike-wave discharges and its pharmacological profile seem to be identical in the two models. The primary purpose of the present paper is to describe some characteristics of the frontal and occipital sleep spindles and spike-wave discharges in WAG/Rij rats. The second purpose is to investigate pharmacological properties of these EEG transient phenomena. Three commonly used drugs known to be sensitive for sleep spindles were used: the barbiturate phenobarbital, the benzodiazepine flunitrazepam and the noradrenergic alpha-2 agonist clonidine. Although drug effects on some of these EEG phenomena were earlier studied (Kleinlogel et al. 1975, Peeters et al. 1988, Coenen and van Luijtelaar 1989, Buzsáki et al. 1991), sleep spindles and spike-wave discharges have not been investigated together and at the same time in rats. The results might shed some light on recent theories on the thalamic pacemaker of sleep spindles and spike-wave discharges (Steriade and Llinás 1988, Steriade and Buzsáki 1990).

METHODS

One year old male WAG/Rij rats served as subjects. They were housed in groups until surgery, then they were singly housed. At the time of surgery they weighed between 307 and 384 g. Animals were maintained on a 12-12 h light-dark (LD) regime, with white lights on at 20.00 h. The experiment took place in freely moving animals during the dark phase of the LD cycle and drugs were always given at 11.00 h.

Two EEG electrode sets were permanently implanted under pentobarbital anesthesia (60 mg/kg). Two frontal electrodes connected to a bipolar electrode set (Plastic One, MS 303/1) were placed at coordinates A 2.0, L 2.1 and A 2.0, L 1.9 respectively. Two other electrodes belonging to a tripolar set (Plastic One, MS 333/2-A) were placed on area 17 (occipital cortex) with coordinates A -5.5, L 2.1 for the first, and A -5.5, L 2.3 for the second electrode. The ground electrode was placed above the cerebellum. All coordinates were measured in mm with skull surface flat and bregma 0.0. This set-up allowed the recording of a local frontal and occipital EEG. Following surgery, subjects were allowed to recover for at least 10 days.

Phenobarbital, flunitrazepam and clonidine were intraperitoneally injected at a volume of 2 ml/kg body weight. Rats were random chosen from the population of operated animals. Phenobarbital ($n = 8$) was injected in a dose of 20 mg/kg, flunitrazepam ($n = 6$) in a dose of 0.188 mg/kg, and clonidine ($n = 7$) in a dose of 0.00625 mg/kg. Control groups for phenobarbital and clonidine

received saline, the control group for flunitrazepam received its solvent, a mixture of propyleneglycol (40%), ethanol (10%), sodiumbenzoate (5%) and distilled water (45%) in the same volume. The wash-out period was at least one week.

The animals were connected to the recording leads for adaptation 16 h prior to the base-line recording. The base-line was always recorded between 10.00 and 11.00 h (n = 10), drug and solvent injections always occurred at 11.00 h. All EEG sessions lasted one hour.

The EEG signals were amplified and filtered by an Elema-Schönander polygraph and frequencies between 1 and 70 Hz were allowed to pass. In order to facilitate the detection of sleep spindles the frontal and occipital EEG was led through a band-pass filter 7 Hz (24 dB/oct) - 14 Hz (30 dB/oct). The EEG's were subsequently stored in digitised form on a magneto-optical disk (DATA Instruments, AT-CODAS). Spike-wave discharges were visually scored according to criteria described earlier (for examples see van Luijtelaar and Coenen 1986). In brief, the minimum duration of a group of sharp peaks and slow waves must be one second, the amplitude of the spikes must be twice the amplitude of the background EEG, the frequency of the spike-wave discharges must be between 7.5 and 11 Hz and the morphology must be asymmetrical with respect to the base-line. Sleep spindles were also analysed visually and scoring was facilitated by the 7-14 Hz band-pass filter. Sleep spindles were identified if there was a group of rhythmic waves in the band pass filtered EEG channel which had to be symmetrical, a waxing and waning morphology with round peaks and valley's with a frequency between 8 and 14 Hz without a concomitant of spike-wave discharges in the normal (1-70 Hz) channel. The minimal duration had to be larger than 0.5 s. It had to be admitted that is was sometimes difficult to quantify the different types of EEG oscillations. There were also EEG oscillations not completely fulfilling the criteria for spike-wave discharges. For reasons of clarity it was decided not to report them.

RESULTS

Both frontal and occipital sleep spindles were found; although both type of sleep spindles showed the progressively increasing then decreasing amplitude envelop, the ideal shape was not always present (see also Jankel and Niedermeyer 1985). Frontal spindles had a larger amplitude than the occipital spindles. An over-

TABLE I

Number and duration of frontal and occipital sleep spindles (A) and spike-wave discharges (B) during the base-line period. Total number and divided into three subcategories (1) the EEG transient is restricted to that area, (2) another type of EEG transient is concomittantly present in the other EEG lead, (3) a similar type of transient is concomittantly present in the other EEG lead, are given

A: Sleep spindles			
Frontal sleep spindles		Occipital sleep spindles	
Total number	25.7 ± 2.1	Total number	15.6 ± 2.9
mean duration	1.0 ± 0.0	mean duration	0.8 ± 0.0
spindles restricted to frontal area:		spindles restricted to occipital area:	
number	23.7 ± 3.8	number	9.9 ± 1.5
mean duration	0.9 ± 0.0	mean duration	0.7 ± 0.1
spindles with concomitant: occipital SWD:		spindles with concomitant frontal SWD:	
number	0.1 ± 0.1	nummer	3.9 ± 0.8
mean duration	0.3 ± 0.2	mean duration	0.8 ± 0.2
spindles with concomitant occipital spindle:		spindles with concomitant frontal spindle:	
number	1.9 ± 0.6	number	1.8 ± 0.6
mean duration	1.0 ± 0.1	mean duration	0.7 ± 0.2
B: Spike-wave discharges (SWD)			
Frontal SWD		Occipital SWD	
Total number	20.5 ± 6.7	Total number	2.8 ± 2.3
mean duration	6.6 ± 0.3	mean duration	1.0 ± 0.2
SWD restricted to frontal area:		SWD restricted to occipital area:	
number	15.8 ± 3.8	number	1.3 ± 0.3
mean duration	5.7 ± 0.8	mean duration	1.0 ± 0.1
SWD with concomitant occipital SWD:		SWD with concomitant frontal SWD:	
number	0.8 ± 0.4	nummer	1.0 ± 0.2
mean duration	2.0 ± 2.2	mean duration	1.0 ± 0.2
SWD with concomitant occipital spindle:		SWD with concomitant frontal spindle:	
number	3.7 ± 2.0	number	0.1 ± 0.1
mean duration	4.7 ± 1.1	mean duration	1.0 ± 0.1

view of the data obtained under base-line condition is presented in Table I. T-tests for dependent groups showed that there were more frontal than occipital sleep spindles: 25.7 ± 2.1 (mean and SEM) vs. 15.9 ± 2.9 ($P<0.05$). Frontal sleep spindles were only rarely (8%) accompanied by a concomitant occipital sleep spindle or a spike-wave discharge.

Occipital sleep spindles were in 36% accompanied by a frontal oscillation, most often a spike-wave discharge. It was also clear that frontal and occipital sleep spindles could occur independently. The mean duration of the frontal spindles was 1.0 ± 0.1 s, the occipital spindles were slightly shorter 0.8 ± 0.1 s ($P<0.05$).

The number of spike-wave discharges in the base-line period was 20.5 ± 6.7, the mean duration was 6.6 ± 0.3 s. These spike-wave discharges were pre-dominantly (77%) restricted to the frontal lead. Occasionally a frontal spike-wave discharge was accompanied by an occipital sleep spindle. There were only a few occipital spike-wave discharges: 2.8 ± 2.3. The mean duration of the occipital spike-wave discharges (1.0) was shorter ($P<0.01$) than the mean duration of the frontal spike-

TABLE II

Drug effects on sleep spindles and spike-wave discharges. Mean number and SEM of frontal and occipital spindles and spike-wave discharges (SWDs) after control (C) injection and after one of the following drugs (D): phenobarbital, flunitrazepam and clonidine, all were administered i.p.

	Frontal Spindles		Occipital Spindles	
	C	D	C	D
Drug				
Phenobarbital ($n = 8$)				
number	29.0 ± 5.5	64.3 ± 10.2**	18.5 ± 6.6	11.5 ± 5.9
duration	0.9 ± 0.0	1.0 ± 0.0	0.7 ± 0.2	0.6 ± 0.2
Flunitrazepam ($n = 6$)				
number	16.0 ± 2.4	58.3 ± 7.9**	10.3 ± 7.4	9.3 ± 3.6
duration	0.8 ± 0.1	0.9 ± 0.0	0.6 ± 0.4	0.8 ± 0.1
Clonidine ($n = 7$)				
number	21.8 ± 5.4	9.1 ± 0.7**	18.7 ± 8.2	63.5 ± 15.9*
duration	0.9 ± 0.0	0.9 ± 0.1	0.7 ± 0.2	1.3 ± 0.1**
	Frontal SWDs		Occipital SWDs	
Phenobarbital				
number	22.2 ± 7.0	4.1 ± 1.3**	1.8 ± 1.6	1.9 ± 1.2
duration	6.9 ± 0.6	2.1 ± 0.5**	0.8 ± 0.4	0.5 ± 0.2
Flunitrazepam				
number	25.3 ± 0.4	7.5 ± 1.3***	2.7 ± 2.7	3.0 ± 1.5
duration	6.4 ± 0.3	2.9 ± 0.5**	0.9 ± 0.6	1.3 ± 0.3
Clonidine				
number	25.5 ± 5.6	75.4 ± 9.8***	3.0 ± 2.3	8.0 ± 5.4
duration	6.6 ± 0.3	7.4 ± 0.5	0.7 ± 0.4	1.3 ± 0.8

Statistical (t-test for independent groups) difference between control and drug: *$P<0.05$, ** $P<0.01$, *** $P<0.001$.

wave discharges. Spike-wave discharges were rarely present at the occipital site only.

An overview of the results of the effects of the three drugs is presented in Fig. 1 and Table II. In some of the categories of EEG transients no or only a few transients were found. Therefore only the categories with a substantial number of EEG transients are presented in Table II. Since the drug injected animals were not the same subjects as in the control group, *t*-tests for independent groups were used.

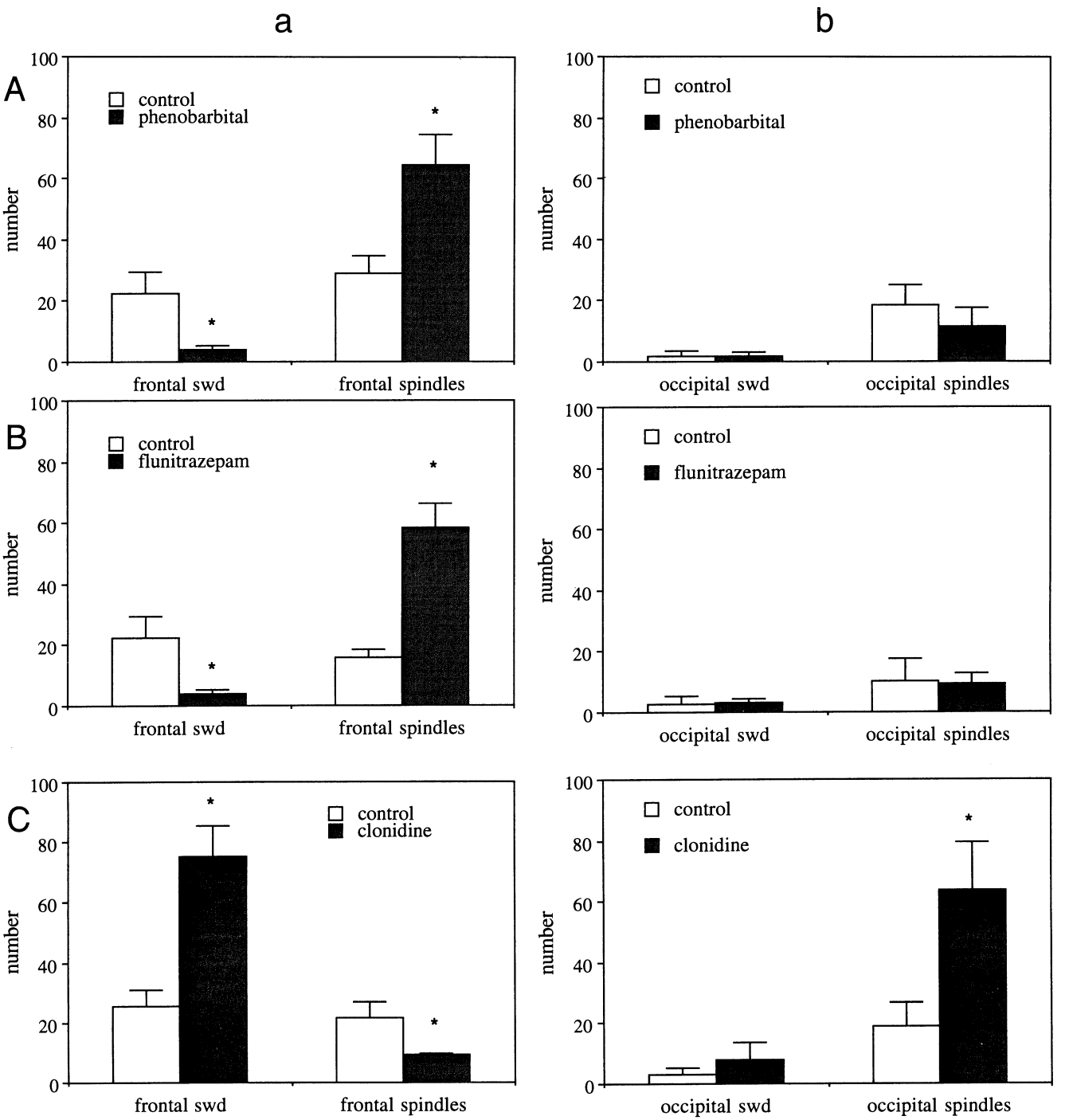

Fig. 1. a, drug effects on number of frontal sleep spindles and frontal spike-wave discharges (swd). After A, phenobarbital; B, flunitrazepam; C, clonidine; b, drug effects on number of occipital sleep spindles and occipital spike-wave discharges. After A, phenobarbital; B, flunitrazepam; C, clonidine. Depicted are mean and SEM.

In rats which received phenobarbital, the number of frontal spike-wave discharges ($P<0.01$) was smaller compared to its own control group. On the other hand, the number of frontal sleep spindles was higher after phenobarbital than after the control injection ($P<0.01$). The rats which had received phenobarbital showed a shorter mean duration of the spike-wave discharges ($P<0.01$) than the control rats. The number and duration of the occipital sleep spindles was not different for the phenobarbital and control group.

After flunitrazepam the number ($P<0.001$) and duration ($P<0.01$) of the frontal spike-wave discharges was lower than in the control group. The number of frontal sleep spindles ($P<0.05$) was higher than in the control group. The number and duration of occipital sleep spindles was not different for the flunitrazepam and control group.

After clonidine the number ($P<0.01$) of frontal spike-wave discharges was higher that the control group, the number of frontal sleep spindles ($P<0.01$) was lower than that in the control group. The number ($P<0.05$) and duration ($P<0.01$) of occipital sleep spindles was higher after clonidine than after the control injection.

The EEG oscillations not completely fulfilling the criteria for spike-wave discharges showed the same drug effects as the spike-wave discharges.

DISCUSSION

Two types of sleep spindles were found in WAG/Rij rats. The vast majority of the frontal spindles was seen without an occipital EEG oscillation and only in 7.8% of the cases, a frontal spindle was accompanied by an occipital spindle. In contrast, occipital spindles were often accompanied (61.3%) by a frontal oscillation. These data confirm and extend the results described by Terrier and Gottesmann (1978). These authors emphasised the existence of the two types of independently occurring sleep spindles. Now this is also found in this particular inbred strain of rats. The existence of different types of sleep spindles in humans is acknowledged by quite a few authors (Gibbs and Gibbs 1950, Matsubayashi et al. 1981, Hori et al. 1990, Scheuler et al. 1990, Scheuler 1990-1991, Jobert et al. 1992). The independence of the frontal and occipital spindles was one of the reasons for Gandolfo et al. (1985) to assume the existence of two different pace-makers for sleep spindles in rats: one in the thalamus and one in the hippocampus.

Spike-wave discharges predominantly occurred in the frontal EEG, while independently occurring occipital spike-wave discharges were much less often present. Rarely, an independently occurring occipital spike-wave was found, identical with respect to morphology as described earlier, then it was described as a type II phenomenon (van Luijtelaar and Coenen 1986). A striking difference between the frontal and these occipital spike-wave discharges is, besides the direction of the peaks, that frontal spike-wave discharges last about five times as long as type II, occipital spike-wave discharges. It needs to be emphasised that two active electrodes were at a distance of 1.5 mm. When the active electrodes are widely apart it can be demonstrated that spike-wave discharges are generalized with a large involvement of the frontal, central and parietal rather than the occipital region (Buzsáki et al. 1988, van Luijtelaar and Coenen 1989).

The drugs induced mainly significant effects on the number of EEG transients, although sometimes also the mean duration was changed. Generally, the effects on duration went in the same direction as the effects on the number. Drug effects on sleep spindles will be discussed first, followed by effects on spike-wave discharges. Phenobarbital increased the number of frontal sleep spindles and no change in the number of occipital spindles was found. The first effect is well known: barbiturates are traditionally used to evoke sleep spindles in cats (Gottesmann 1964, Andersen et al. 1967, Gusselnikov et al. 1973). Now it seems that only frontal sleep spindles are sensitive for barbiturates considering the lack of response of the occipital sleep spindles. Although in man spindle augmentation occurs after barbiturates (Soldatos et al. 1977), it needs to be established whether occipital sleep spindles are also not sensitive for barbiturates, as was found here. Also the benzodiazepine flunitrazepam augmented the number of sleep spindles in the present study. This is in agreement with many other studies in different species (Gusselnikov et al. 1973, Monti and Altier 1973, Johnson et al. 1976, Soldatos et al. 1977, Scheuler 1990-1991, Gandolfo and Gottesmann 1991, Jobert et al. 1992). And again, the occipital sleep spindles were unaltered. Of interest is that Scheuler (1990-1991) found that frontal sleep spindles are more sensitive for the effects of benzodiazepines that occipital sleep spindles, suggesting that frontal sleep spindles have different pharmacological characteristics than occipital sleep spindles. In the light of Scheuler's result it is not surprising that frontal and occipital sleep spindles have a different pharmacological profile in rats as well. This was actually also found after clonidine. This drug reduced the number of frontal sleep spindles, in agreement with ear-

lier results (Kleinlogel et al. 1975), but an opposite reaction was found for the number of occipital sleep spindles: its number was enhanced after clonidine. It was the only drug used in this experiment which modulates occipital sleep spindles.

Spike-wave discharges were suppressed by flunitrazepam and phenobarbital and this in agreement with previous results obtained with barbiturates and benzodiazepines (Peeters et al. 1988, Coenen and van Luijtelaar 1989). Spike-wave discharges were found to be enhanced after clonidine. This confirms the results of the Buzsáki et al. 1991 study. The occipital spike-wave discharges were small in number and did not seem to be enhanced by any of the drugs.

The three different drugs induce inverse effects on the number of frontal EEG oscillations: the increase in the number of sleep spindles induced by flunitrazepam and phenobarbital is accompanied by a decrease in the number of spike-wave discharges and the decrease in the number of sleep spindles induced by clonidine is accompanied by an increase in the number of spike-wave discharges. This suggests a reciprocal relationship between frontal sleep spindles and spike-wave discharges. The present data are the first which showed an inverse relationship between the number of frontal sleep spindles and spike-wave discharges in rats. Kellaway et al. (1990) found also a reciprocal relationship between spindles and spike-wave discharges in a clinical study.

In the present study it was also found that the pharmacological properties of occipital sleep spindles are different from the properties of the frontal sleep spindles. Occipital sleep spindles were not effected by the barbiturate or the benzodiazepine, their occurrence was facilitated by the alpha-2 agonist clonidine. Frontal sleep spindles are sensitive for barbiturates and benzodiazepines. Occipital spike-wave discharges were small in number and there were no drug effects. In contrast to what has been found for the frontal sleep spindles, there is no reciprocal relationship between occipital sleep spindles and occipital or the total number of spike-wave discharges.

The present data might have some consequences for theories about the thalamic pace-maker in cats and rodents. A single thalamic pace-maker is assumed for spike-wave discharges and sleep spindles (Steriade and Llinás 1988, Steriade and Buzsáki 1990, Buzsáki 1991), although Steriade studied EEG oscillations in cats which don't have spontaneously occurring spike-wave discharges. Also based on the work of Gloor (1995) in cats, assuming that spike-wave discharges are indeed transformed sleep spindles and assuming that sleep spindles and spike-wave discharges have a common pacemaker, one might expect an inverse relationship between the number of sleep spindles and spike-wave discharges. The presently found inverse relationship between the number of (frontal) sleep spindles and spike-wave discharges might fit into this view. However, the presence of independently occurring occipital sleep spindles and the differential sensitivity of clonidine for occipital sleep spindles do not fit into a one pacemaker theory. In order to explain this, one must assume either a second pacemaker or at least a second occipital sleep spindle control system. The localisation of the second pace-maker is unknown and even a thalamic origin is not certain since synchronisation of thalamic units is rather general although there are parts of the thalamus (anterior part and epithalamus) which are naturally deprived of afferents from the reticular thalamic nucleus (Steriade and Llinás 1988). Thalamic lesion studies are needed to investigate whether frontal and occipital EEG oscillations are both under the control of the same pacemaker.

In all, our data confirm the existence of two types of sleep spindles in the rat. Besides a different topographical organisation they seem to have a distinct pharmacological profile. The frontal sleep spindles are sensitive for barbiturates and benzodiazepines, occipital sleep spindles are sensitive for clonidine. Frontal sleep spindles show an inverse relationship with spike-wave discharges in accordance with major theories on the origin of cortical EEG oscillations in cats and rats. The increase of occipital sleep spindles after clonidine does not seem to fit easily into a single pace-maker model.

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REFERENCES

Andersen P., Andersson S.A., Lomo T. (1967) Some factors involved in the thalamic control of spontaneous barbiturate spindles. J. Physiol. 192: 257-281.

Buzsáki G. (1991) The thalamic clock: emergent network properties. Neuroscience 41: 351-364.

Buzsáki G., Bickford R.G., Ponomareff G., Thal L.J., Mandel, R.J., Gage F.H. (1988) Nucleus basalis and thalamic control of neocortical activity in the freely moving rat. J. Neurosci. 8: 4007-4026.

Buzsáki G., Kennedy, B., Solt, V.B., Ziegler M. (1991) Noradrenergic control of thalamic oscillation: the role of a2 receptors. Eur. J. Neurosci. 3: 222-229.

Coenen A.M.L., Drinkenburg W.H.I.M., Inoue M., Van Luijtelaar E.L.J.M. (1992) Genetic models of absence epilepsy, with emphasis on the WAG/Rij strain of rats. Epilepsy Res. 12: 75-87.

Coenen A.M.L., Drinkenburg W.H.I.M., Peeters B.W.M.M., Vossen J.M.H., van Luijtelaar E.L.J.M. (1991) Absence epilepsy and the level of vigilance in rats of the WAG/Rij strain. Neurosci. Biobehav. Rev. 15: 259-263.

Coenen A.M.L., van Luijtelaar E.L.J.M. (1989) Effects of diazepam and two beta-carbolines on epileptic activity and on EEG and behavior in rats with absence seizures. Pharmacol. Biochem. Behav. 32: 27-35.

Gandolfo G., Glin L., Gottesmann C. (1985) Study of sleep spindles in the rat: a new improvement. Acta Neurobiol. Exp. 45: 151-162.

Gandolfo G., Gottesmann C. (1991) Effects of benzodiazepines on intermediate stage and paradoxical sleep. Sleep Res 20A: 134.

Gibbs F.A., Gibbs E.L. (1950) Atlas of electroencephalography. Vol 1. Reading, MA: Addison-Wesley.

Gloor P. (1979) Generalized epilepsy with spike-and-wave discharge: a reinterpretation of its electrographic and clinical manifestations. Epilepsia 20: 571-588

Gloor P. (1995) Feline generalised penicillin epilepsy: extrapolations to neurophysiological mechanisms in humans. In: Typical absences and related epileptic syndromes (Eds. J.S. Duncan and C.P. Panayiotopoulos). Churchill Communications, London, p. 74-83.

Gloor P., Fariello F.G. (1988) Generalized epilepsy: some of its cellular mechanisms differ from those of focal epilepsy. TINS 11: 63-68.

Gloor P., Pellegrini A., Kostopoulos G.K. (1979) Effects of changes in cortical excitability upon the epileptic bursts in generalized penicillin epilepsy of the cat. Electroencephalogr. Clin. Neurophysiol. 46: 274-89.

Gottesmann C., Change C. (1964) Données sur l'activité corticale au cours du sommeil profond chez le rat. C.R.Soc Biol Paris 158: 1829-1834.

Gusselnikov V.I., Iznak A.F., Mukhametov L.M. (1973) Neuronal activity of nucleus caudatus and thalamus during barbiturate spindles in rats. Electroencephalogr. Clin. Neurophysiol. 35: 523-531.

Hori T., Hayashi M., Morikawa T. (1990) Topography and coherence analysis of the hypnogogic EEG. In: Sleep'90 (Ed. J. Horne). Pontenagel Press, Bochum, p. 10-12.

Jankel W.R., Niedermeyer E. (1985) Sleep spindles. J. Clin. Neurophysiol. 2: 1-35.

Jobert M., Poiseau E., Jähnig P., Schulz H., Kubicki S. (1992) Topographical analysis of sleep spindle activity. Neuropsychobiol. 26: 210-217.

Johnson L.C., Hanson K., Bickford R.G. (1976) Effect of flurazepam on sleep spindles and K-complexes. Electroencephalogr. Clin. Neurophysiol. 40: 67-77.

Kellaway P., Frost J.D., Crawley J.W. (1990) The relationship between sleep spindles and spike-wave bursts in human epilepsy. In: Generalized epilepsy: neurobiological approaches (Eds. M. Avoli, P. Gloor, G. Kostopoulos and R. Naquet). Birkhäuser, Boston, p. 36-48.

Kleinlogel H., Scholtysik G., Sayers A.C. (1975) Effects of clonidine and BS 100-141 on the EEG sleep pattern in rats. Eur. J. Pharmacol.33: 159-163.

Kostopoulos G., Gloor P. (1982) A mechanism for spike-wave discharge in feline penicillin epilepsy and its relationship to spindle generation. In: Sleep and epilepsy (Eds. M.B. Sterman, M.N. Shouse and P. Passouant). Academic Press, New York, p. 11-27.

Marescaux C., Micheletti G., Vergnes M., Depaulis A., Rumbach L., Warter J.M. (1984) A model of chronic spontaneous petit mal-like seizures in the rat: comparison with pentylenetetrazol-induced seizures. Epilepsia 25:326-331.

Matsubayashi K., Ishiyama Y., Homma I., Ebe, M. (1981) Some characteristics of sleep spindles derived from automatic analysis. Sleep 4: 392-399.

Monti J.M., Altier H. (1973) Flunitrazepam (Ro 5-4200) and sleep cycle in normal subjects. Psychopharmacology (Berl.) 32: 343-349.

Peeters B.W.M.M., Spooren W.P.J.M., van Luijtelaar E.L.J.M., Coenen A.M.L. (1988) The WAG/Rij model for absence epilepsy: anticonvulsant drug evaluation. Neurosci. Res. Comm. 2: 93-97.

Scheuler W., Kubicki St., Scholz G., Marquardt J. (1990) Two different activities in the sleep spindle frequency band-discrimination based on the topographical distribution of spectral power and coherence. In: Sleep'90 (Ed. J. Horne). Pontenagel Press, Bochum, p. 13-16.

Scheuler W. (1990-1991) EEG sleep activities react topographically different to GABAergic sleep modulation by flunitrazepam: relationship to regional distribution of benzodiazepine receptor subtypes? Neuropsychobiology 23: 213-221.

Soldatos C.R., Bixler E.O., Scharf M.B., Kales A. (1977) Sleep spindles, rapid eye movements and EEG fast activity and long term administration of flurazepam and pentobarbital: further studies. Sleep Res.: 6:84.

Steriade M., Buzsáki G. (1990) Parallel activation of thalamic and cortical neurons by brainstem and basal forebrain cholinergic systems. In: Brain cholinergic systems (Eds. M. Steriade and D. Biesold). Oxford Medical Press, Oxford, p. 3-64.

Steriade M., Contreras D., Amzica F. (1994) Synchronized sleep oscillations and their paroxyxmal developments. TINS 17: 199-208.

Steriade M., Llinás R.R. (1988) The functional states of the thalamus and the associated neuronal interplay. Physiol. Rev.: 68: 649-742.

Steriade M., McCormick D.A., Sejnowski (1993) Thalamocortical oscillations in the sleeping and aroused brain. Science 262: 679-685.

Terrier G., Gottesmann C. (1978) Study of cortical spindles during sleep in the rat. Brain Res. Bull. 3: 701-706.

von Krosigk M., Bal T., McCormick D.A. (1993) Cellular mechanisms of a synchronized oscillation in the thalamus. Science 261: 361-364.

van Luijtelaar E.L.J.M., Coenen A.M.L. (1986) Two types of electrocortical paroxysms in an inbred strain of rats. Neurosci. Lett. 70: 393-397.

van Luijtelaar E.L.J.M., Coenen A.M.L. (1989) The WAG/Rij model for generalized absence seizures. In: Advances in epileptology (Eds. J. Manelis et al.). Vol 17. Raven Press, New York, p. 78-83.

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