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Expression of Epileptiform Activity Induced by a Penicillin Focus Within the Posterior Thalamus in the Awake Rat

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HORN, E. AND B. GEHRING. *Expression of epileptiform activity induced by a penicillin focus within the posterior thalamus in the awake rat.* PHARMACOL BIOCHEM BEHAV **54**(4) 759–770, 1996.—Investigations were performed to study the epileptiform activity, induced by a local injection of penicillin (PCN) into the posterior thalamus (pTh) of the awake rat, and to compare it with the epilepsy induced in the same animals 2 weeks later by an injection of PCN into the motor cortex (MC). Using EEG recordings, 1) the distribution of focal cortical activity, and 2) the severity of the epileptiform activity (frequency of focal activity, occurrence and duration of generalized episodes) were analyzed. The focal activity of pTh rats was characterized by two types of potentials: (a) sharp potentials with a spike-like shape that developed during the first hour after PCN injection only in the visual cortex, but in the transition area between the motor and sensory cortex during the last period of epileptiform activity; and (2) large potentials with a wave- or spike-wave-like shape that had their center of focal expression in the transition zone between the motor and sensory cortex. MC rats exhibited only a spike-like potential with or without short-lasting afterdischarges in the homotopic areas of the MC of both hemispheres. During periods with large potentials only, the number of generalized episodes was significantly reduced with respect to those periods with sharp potentials. When the epileptiform activity changed from large to sharp potentials, the interictal frequency increased significantly. It is postulated (a) that a pTh focus activates the lateral and/or the reticular thalamic areas, which, due to their high intrinsic potential for synchronization, cause a self-sustained interictal activity of the large potential type; and (b) that the wave of the large potentials is involved in an anticonvulsive mechanism that reduces the extent of ictal as well as interictal activity.

Anticonvulsive mechanism Generalized seizures Interictal activity Motor cortex Penicillin Posterior thalamus Rat

DESPITE the postulation that thalamic areas are insensitive to the epileptogenic action of topically (13,14) or systemically applied penicillin (31), experimental work in animals and observations in man made clear that thalamic structures are involved in mechanisms leading to generalized epilepsy. The epileptogenic properties of the thalamus were considered as lower as those of the cerebral cortex. In humans, the incidence of epilepsy was 8% in case of thalamic tumours but 55% for cerebral cortex tumours (39). In monkeys (*Macaca mulatta*), a significant sensitivity of several thalamic nuclei was described (9) 20 years before the first report of Gloor and his co-workers. Anatomical (7,11,26), pharmacological (21,23), physiological (6,8,12,24,29), and biochemical (40) data, obtained during the last years, have strengthened the importance of thalamic nuclei on the initiation and performance of convulsive activity. The medial nuclei and the reticular thalamic structures were considered as the most responsible ones [cf. (39)]. Some thalamic structures mainly located in the lateral (8) and reticular (29) nuclei were characterized by a high developed potency for synchronized activation [cf. (32)].

The importance of the thalamus in the epileptic syndrome is obviously correlated with its extensive projection to cortical and other areas. Some of the thalamic nuclei form rather specific connections while other thalamic nuclei project in a wide-spread manner. Specific projections were described for the anterior nuclei to the cingulate cortex and the hippocampal region [cf. (10)], whereas the mediodorsal nucleus that projects to the frontal pole of the cortex is mainly connected to the dorsal lip of the rhinal sulcus, medial cortical areas, and some subcortical regions. The efferent connections of the ventrolateral thalamic area are directed to the motor cortex MI. The venteroposterior nuclei are reciprocally connected in a topographical manner with SI and SII. The lateral nuclear groups LP and LD project to both the cingulate and

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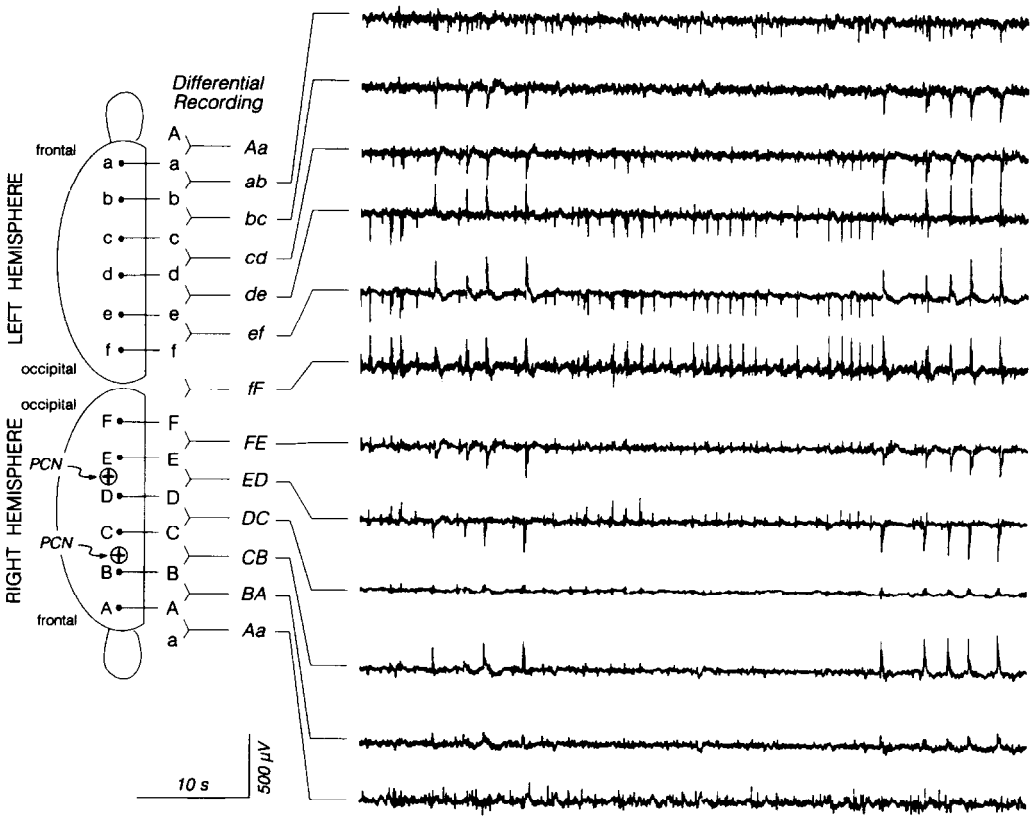

FIG. 1. Differential recordings from 12 cortical electrodes and definition for the determination of the site of maximal focal activation. Left: location of the electrodes on the left (small letters) and right hemisphere (capital letters). Middle: definition of the differential recordings between adjacent electrodes. Right: original EEG recorded during the period of the disappearence of sharp potentials and the development of large potentials. Note the different sites of high focal activation for both potential types. Large potentials developed in the transition zone between the sensory cortex and the motor cortex of both hemipheres at d and between D and C. Sharp potentials occur in the left occipital cortex at electrode f. PCN, cortical penetration sites for the intrathalamic (between D and E) and intracortical (between B and C) PCN injections.

visual cortex, for instance, to occipital cortical areas [cf. (10,41)].

A diffuse cortical projection was described for the posterior thalamic nuclei [cf. (10)]. The demonstration of its epileptogenic properties in the cat (27) makes the posterior thalamic nucleus attractive to establish an epileptic focus and to investigate (a) the type of epileptiform activity and, in particular, (b) the expression of cortical focal activation patterns because these patterns may be closely related to the site of the primary focus. In fact, a penicillin focus within the olfactory cortex elicited multifocal activity patterns in nonhomotopic cortical sites including the most frontal and occipital areas, while a penicillin focus within the motor cortex induced either a unifocal pattern or, more frequently, a bifocal one in homotopic areas of both hemispheres (16). The close connection between the cerebral cortex and thalamic nuclei and the observation of a good correlation between thalamic and cortical spindles of anatomically linked areas (4) makes it likely that thalamic activity can be recorded by the cortical EEG. Therefore, the aim of this study was, to describe the epileptogenic sensitivity of this area by means of the cortical EEG quantitatively. As a reference approach, the epileptiform activation was also induced in the motor cortex because a penicillin focus in this area induced a mirror focus (16) due to its direct anatomical projection to the homotopic area of the contralateral hemisphere.

METHOD

Animals

The study was performed with male Wistar rats from the stock of the Animal Research Center of the University of Ulm (Germany). Animals were kept under a 12 L:12 D rhythm for their whole life. They were prepared for the experiments when they were 8 to 10 months old. Under pentobarbital anesthesia (Nembutal; 55 to 120 mg/kg body weight, IP), two guiding tubes with an inner diameter of 0.4 mm were fastened to the skull. One of them was used for the local intrathalamic penicillin (PCN) injection, the other for the PCN injection into the motor cortex. Additionally, 12 spherical AgAgCl electrodes (diameter 0.3 mm) were attached to the skull, 0.4 mm above the dura. For each hemisphere, they were placed 2.5 mm apart of each other between the stereotaxic coordinates A5 and P7.5 (with respect to bregma) and R2/L2 (right/left frontal areas) to R3/L3 (right/left occipital areas). For at least 4 weeks each animal was housed individually and handled every second day until the experimental day.

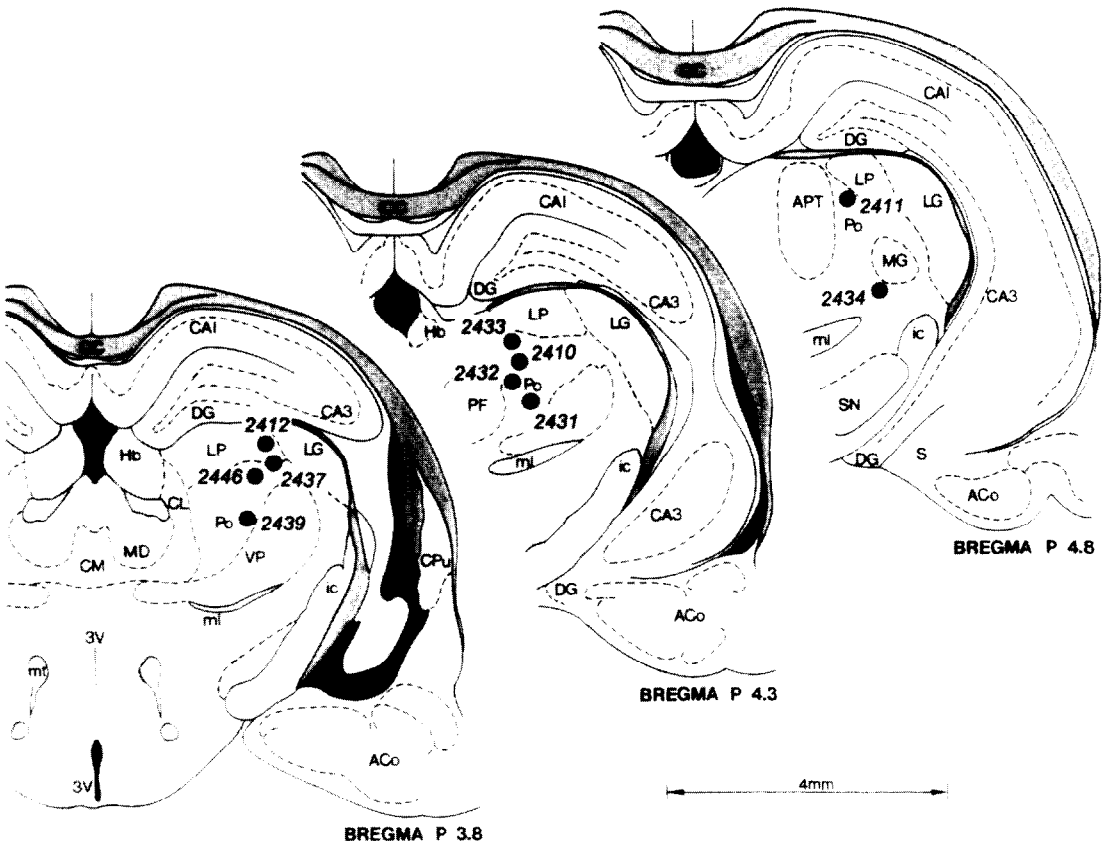

FIG. 2. Penicillin injection sites located within the posterior thalamic area. The stereotaxic sites were determined from the original histological sections and plotted in sections according to the rat brain atlas of (30). Numbers close to the dots indicate the identification number of the individual animals (cf. also Figs. 4 and 5; Table 2). ACo, amygdala complex; APT, anterior tegmental area; CA1 (CA3), field CA1 (CA3) of Ammon's horn; CC, corpus callosum; CL, central lateral thalamic nucleus; CM, central medial thalamic nucleus; CPu, caudate putamen; DG, dentate gyrus; Hb, habenular nucleus complex; ic, internal capsule; LG, lateral geniculate nucleus; LP, lateral posterior thalamic nucleus; MD, mediodorsal thalamic nucleus; MG, medial geniculate nucleus; ml, medial lemniscus; mt, mammillotegmental tract; PF, parafascicular thalamic nucleus; Po, posterior thalamic nucleus group; SN, substantia nigra; VP, ventral pallidum; 3V, third ventricle.

Procedure

Convulsive activity was induced in 10 nonanesthetized rats by an intracerebral injection of 125 IU PCN solved in 0.25 μl of a 0.9% NaCl solution. The outer diameter of the injection cannula was 0.3 mm. During the injection, which usually lasted 3 s, the animals were carefully held in the hand by the experimenter. Injection time was always between 900 and 930 CET. Epileptiform activity was recorded by means of the cortical EEG using differential recordings between adjacent electrodes (Fig. 1). During the recordings, the rats could move freely in a chamber of 25 × 25 × 35 cm^3, standing in a large Faraday box. They could adapt to the experimental condition for 1 h, before PCN was injected. The epileptiform activity was recorded until the last interictal spike was observed. A spike was considered as the last if it was followed by a period of at least 30 min without any epileptiform EEG activity. The rats were videotaped throughout the experiment.

In each rat, epileptiform activity was induced twice. The first injection site was located in the right posterior thalamus (pTh rats). The histological examination from the Nissl-stained brains revealed stereotaxic coordinates of the injection sites between P3.6 and P5.3 (posterior to bregma), R2.3 and R3.3 (right hemisphere), and D4.2 and D6.0 (subdural) [coordinates according to (30)] (Fig. 2). Two weeks later, epileptiform activity was induced for a second time by an injection of PCN into the right motor cortex (pTh/MC rats). The stereotaxic coordinates of these injection sites were between A2.7 and A1.5 (anterior to bregma), R0.8 and R2.3, and between D1.1 and D1.7. The same PCN concentration was used as during the first experiment. By the second investigation, the site specificity of the PCN action was tested.

Data Collection

The EEG recordings were used for two types of analysis. (a) The interictal activity was characterized by the number of potentials per minute (= frequency of interictal activity); the ictal activity by the number and length of seizures, by the seizure frequencies and by the total seizure time. (b) The expression of cortical focal activation was determined using the orientation of cortical epileptiform spikes for the 12 recording channels (cf. Fig. 1). For each minute, the most pronounced focus site was determined and plotted for the whole

TABLE 1

QUANTIFICATIVE DESCRIPTION OF EPILEPTIFORM ACTIVATION INDUCED BY A PCN FOCUS WITHIN THE POSTERIOR THALAMUS (pTh), FOLLOWED TWO WEEKS LATER BY AN EPILEPTIFORM ACTIVITY INDUCED BY A PCN FOCUS WITHIN THE MOTOR CORTEX OF THE SAME RATS (pTh/MC)

	Sites of PCN-Injections		Correlation r Between Data From pTH- and pTh/MC-Rats
	pThp (= pTh-Rats)	MC (= pTH/MC-Rats)	
Interictal Activity			
First potential (s)			
Median	103	87	−0.40
min; max	47; 329	66; 180	
Last potential (min)			
Median	361	211*	−0.20
min; max	175; >475	100; 392	
Potential frequency (n/min)			
Median (large type)	4.5	—	
min; max	1.7; 5.3		
Median (sharp type)	22.5	26.5	−0.16
min; max	0.2; 34.8	18.7; 30.7	
Ictal Activity			
First seizure (s)			
Median	433	409	−0.13
min; max	160; 7396	203; 644	
Last seizure (min)			
Median	146	165	−0.48
min; max	16; 298	82; 325	
Seizure length (s)			
Median	44.4	18.1†	−0.43
min; max	26.0; 81.8	5.7; 30.2	
Total seizure number (n)			
Median	6	53‡	−0.49
min; max	2; 7	20;274	
Total seizure time (s)			
Median	220	1015.5‡	−0.27
min; max	52; 383	378; 2025	
Seizure frequency (n/h)			
Median	1.9	24.5§	0.77§
min; max	0.4; 10.4	7.5; 56.3	

Frequency values for sharp potentials were calculated for the periods between the 1st and 45th min, for large potentials between the 45th and 90th min. Correlations (r) between the values obtained from the 10 animals during pTh and pTh/MC treatment are shown on the right part of the table. Significance levels for differences between pTh- and pTh/MC-samples or for correlations between values from pTh- and pTh/MC-treated rats: *$p < 0.02$; †$p < 0.002$; ‡$p < 0.001$; §$p < 0.01$. $n = 10$ rats.

time of epileptiform activity. A cortical area was defined as a representative focus if it was activated for at least 45 s during 1 min. The videorecordings were used to describe the general behavior during epileptiform activation.

For statistical analysis, the nonparametric U-test from Wilcoxon, Mann and Whitney (37) was used to compare spike- and seizure-related values recorded after the pTh and pTh/MC treatment of the rats. Additionally, calculations were performed to detect correlations between corresponding pairs of values collected from both the pTh- and the pTh/MC-treated rats.

RESULTS

General Pattern of Epileptiform Activity and Expression of Cortical Foci

All rats with a PCN focus within the right posterior thalamic area (pTh rats) intensified their licking, cleaning, or feeding activity. Locomotor activity was mainly directed to the left side during the first hour. Periods of fast circle running developed spontaneously, even from absolute rest and were superimposed by episodes of intensive cleaning activity or foreleg tremor. These behavioral activities were not correlated with EEG changes. However, pTh rats exhibited also episodes of abnormal EEG-correlated behavior, which developed from normal locomotor activity, rest, or sleep and were terminated by strong wet-dog shaking. During these periods, the rats behaved quietly with staring eyes. Due to the EEG changes and the characteristic termination, these episodes were defined as seizures.

The rats were treated for a second time by a PCN injection into the motor cortex, 14 days later. Following this treatment, these pTh/MC rats developed jerk movements that could be unequivocally correlated with discrete potentials of the cortical EEG, and tonic, clonic or tonic–clonic seizures, which correlated in the cortical EEG with sequences of high frequent

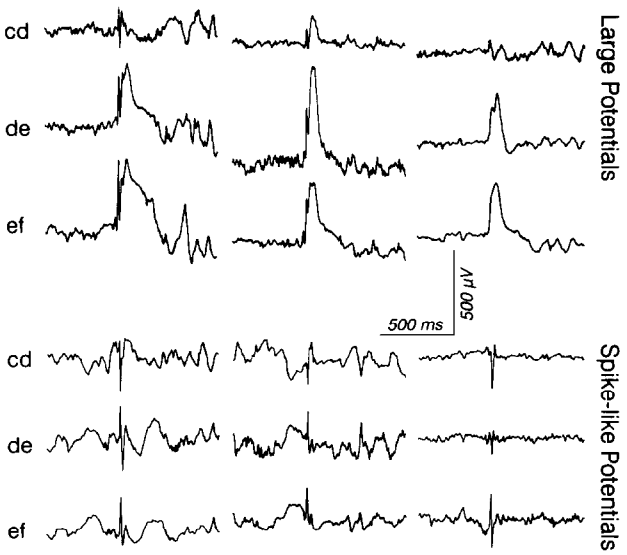

FIG. 3. Potential types recorded by cortical EEG in rats which had a PCN focus within the pTh. Upper plots: large potentials; lower plots: sharp potentials. The potentials were recorded from three different rats (from left to right); they show the extreme expression of the large type. Definition of differential recordings, cf. Fig. 1.

potentials up to 4 Hz during the clonic period and up to 20 Hz during the tonic period.

The pTh-induced epileptiform activity developed rapidly. The first interictal potentials were recorded between the 47th and 329th second (median: 103 s), the first ictal episode between the 160th and 7396th second (median: 433 s). After the additional injection of PCN into the MC (pTh/MC treatment), the first interictal potentials occurred between the 66th and 180th second (median: 87 s), the first ictal episode between the 203rd and 644th second (median: 409 s). Neither the medians for the onset of interictal nor those for the ictal activation differed significantly (Table 1).

The interictal activity of pTh rats lasted between 175 and $>$ 475 min (median: 361 min), the ictal one between 16 and 298 min (median: 146 min). The interictal activity induced by the additional injection of PCN into the MC, 2 weeks later, was significantly shorter (median: 211 min; $p < 0.02$) while the induced ictal episodes disappeared at similar time as after the pTh treatment (median: 165 min; n.s.). The duration values of interictal and ictal activation recorded for the first and second treatment, respectively, were statistically not correlated (Table 1). It is, therefore, likely that the sensitivity of the brain to maintain epileptiform activity depends on the specific properties of the focal area. The different densities of GAD-immunoreactive cell bodies [pTh: $<$ 5%; MC: $>$ 50%; cf. (28)] may be important for this significant sensitivity difference of both areas concerning the duration of interictal activity.

The cortical EEG pattern of pTh rats was characterized by two interictal potential types that differed in shape, frequency (number per minute), and cortical representation. The first type was a spike-like potential (sharp potential) lasting less than 30 ms. Its repetition rates ranged from 0.2 to 58.8 potentials per min (Fig. 3, lower part). The second potential type was composed of a large spike followed by an irregular shaped wave of about the same amplitude (spike-wave-like or large potential). In some instances, only the wave component developed (Fig. 3, upper part). This complex lasted 250 ms to 330 ms; its repetition rate ranged between 1/min and 11/min. Large potentials developed with similar frequencies during resting and waking periods. In 8 of the 10 rats, sharp and large potentials developed simultaneously (cf. Fig. 1, right; Fig. 5), but out of phase with respect to the other type.

The time course for the frequency of interictal potentials was characterized by three periods. A representative example is shown in Fig. 6 (upper plot). In particular, during the first period, either both or only sharp potentials developed at median frequencies of 4.5/min for the large and 22.5/min for the sharp ones (Table 1). This period lasted between 5 and 82 min (median duration 69 min). During the second period, only large potentials developed at frequencies ranging from 1/min to 11/min. This second period lasted between 95 and 325 min (median: 219 min). In six rats, the large potentials disappeared and were followed, during a third period, by a sharp type with repetition rates between 2.2/min and 13.2/min if calculated for 10-min lasting intervals (Figs. 5 and 6).

The expression of cortical focal activation was determined in five rats. Generally, the activated focal areas of the cortex were expressed bilaterally. In rats with a pTh focus, the focal cortical patterns differed for the potential types and the period of interictal activity. Most frequently, a three-period pattern developed as shown exemplarily for an individual animal in Fig. 7. The first period was formed by sharp potentials only. The mean numerical distribution of focal activation determined for the first 70 min after PCN injection showed a large peak at the occipital electrodes F and f and a very low spike activation in the most frontal cortex during this period (Fig. 8, upper left). This occipital focal area shifted between both hemispheres. For the large potentials, the focus was derived from the wave component, which showed a high stability within narrow time intervalls. This potential type was mainly expressed in the transition zone between the sensory and motor cortical area of both hemispheres with some bias to the motor area (Fig. 7; Fig. 8, upper right), even if they were recorded during the first hour after PCN injection. The third period characterized by sharp potentials only showed pronounced focal activation in the transition zone between the motor and sensory area, however, slightly shifted towards the occipital area compared to the representation area of the large potentials (Fig. 8, lower left).

After the injection of PCN into the MC 14 days later, all pTh/MC rats developed a mirror focus. The mean numerical distribution of focal activation centers showed two sharp peaks over the motor cortex of both sides, predominantly at the electrodes B and b. In one rat, a weak supplementary focus developed on the side of the mirror focus (Fig. 8, lower right) at the electrode e. The observations from this second experiment demonstrated that the pecularities of epileptiform activity induced by the PCN injection into the pTh area were specificly related to this site.

State-Dependent Severity of Epileptiform Activity

The severity of interictal activity was described by the median spike frequencies. In the pTh rats, the median frequency for sharp potentials was calculated for the period of 45 min following the PCN injection while that for large potentials was determined from the period between the 45th and 90th min. The corresponding median values were 22.5/min and 4.5/min and differed significantly ($p << 0.001$). The median potential frequency recorded for sharp potentials in the pTh/MC rats was 26.5/min. Thus, it fell into the same range as the

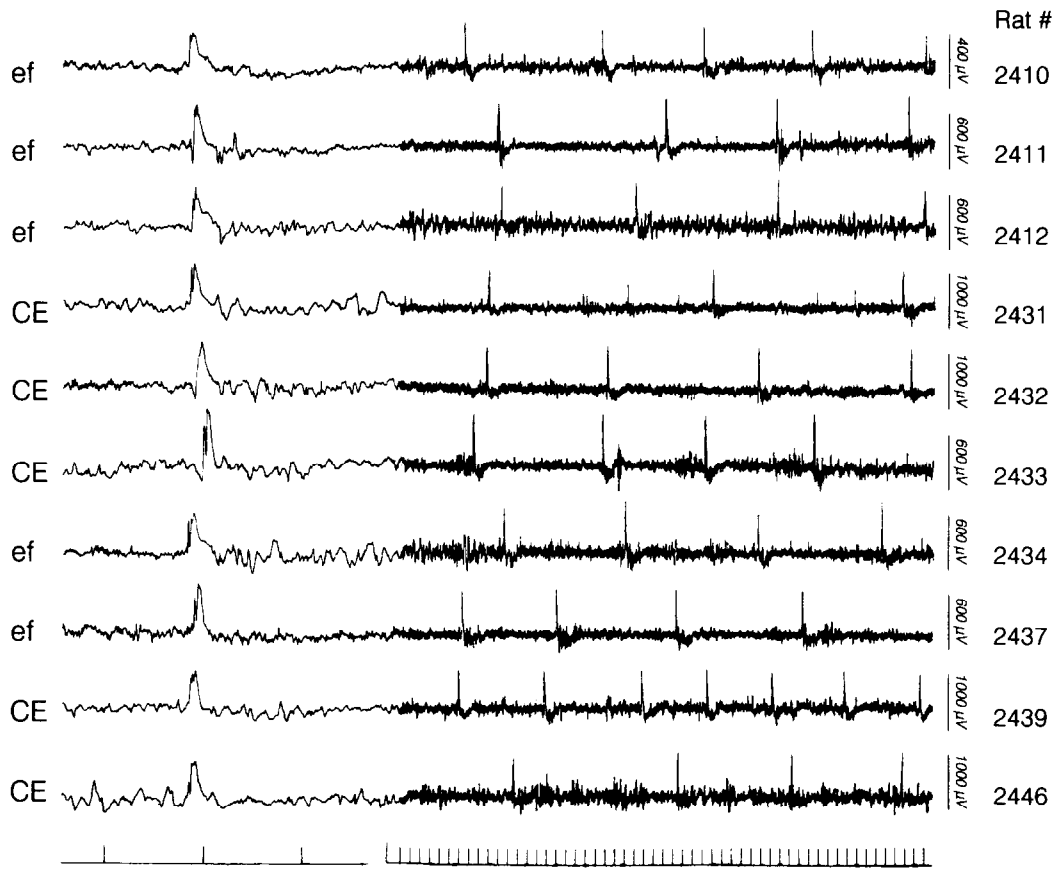

FIG. 4. Representative sequences of large potentials presented for each of the 10 rats of this study. Each period lasts 59 s. Left margin: type of differential recordings; small (capital) letters indicate recordings from the left (right) hemisphere. Note the low frequency of the large potentials. The artefact following the third large potential in the trace of rat 2433 was caused by a severe wet-dog shaking.

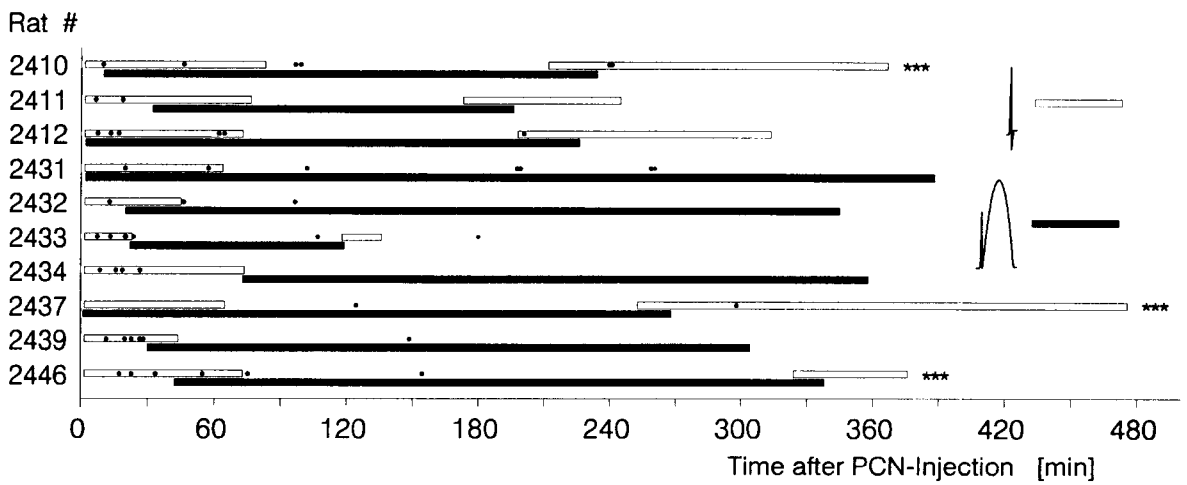

FIG. 5. Duration of the periods at which the sharp and the large interictal potentials were recorded in the cortical EEG. The individual rats are listed from top to bottom (identification number of each rat is given on the left margin). Time zero is time of PCN injection into the pTh (injection sites: cf. Fig. 2). White bars, periods with sharp potentials; black bars, periods with large potentials. Dots within the white bars or above the black ones indicate the onset of a seizure. ***Asterisks indicate that the EEG recording was terminated at this time.

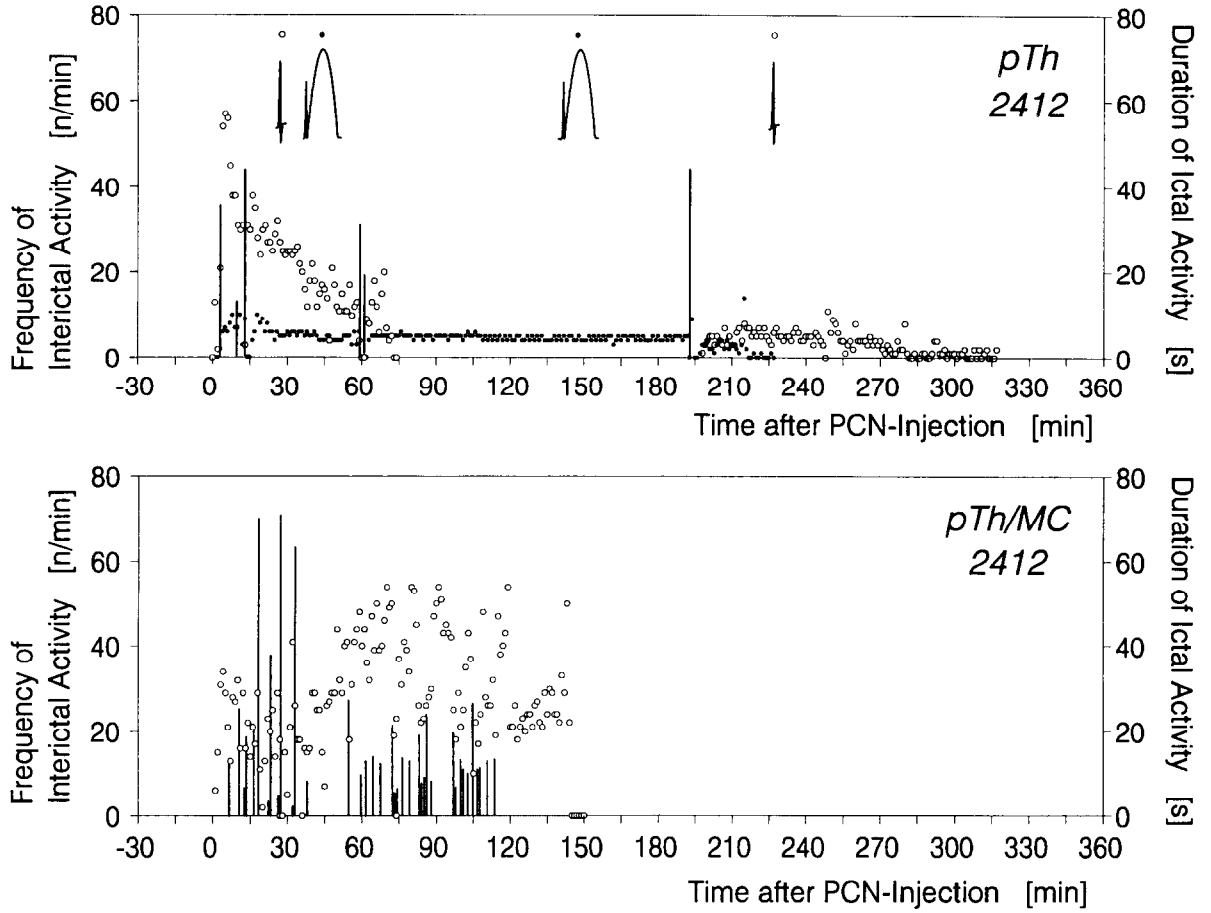

FIG. 6. Time courses of interictal and ictal activity induced by a PCN focus within the posterior thalamus (pTh) or right motor cortex (MC). A representative rat (rat 2412, cf. Fig. 4), which was treated in the right pTh (upper plot), and 2 weeks thereafter in the right MC (pTh/MC) (lower plot). The frequencies of interictal activity were calculated with a time resolution of 1 min and are indicated by the dots (large potentials) and circles (sharp potentials). Vertical bars indicate the onset (= bar position on the time scale) and duration (= bar length) of the generalized seizures. pTh treatment (cf. upper plot): note the significantly lower frequencies for the large potentials (dots) with respect to the sharp ones (circles) which disappear after 75 min. pTh/MC treatment (cf. lower plot): note the significantly higher number of seizures than after injection of PCN into the pTh, and the development of sharp interictal potentials, only.

corresponding value found in the same rats after the injection of PCN into the pTh. Otherwise, there was no significant correlation between the values obtained from the first and the second experiment.

The severity of ictal activity was described by the length and numbers of ictal episodes, by the seizure frequencies and the total seizure time. They demonstrated a significant site specificity. In particular, the median seizure length during pTh epilepsy amounted to 245% of that recorded for the MC-induced epilepsy in the same rat sample. This difference was significant (U-test; $p < 0.002$). The number of seizures was significantly lower for the pTh-induced epilepsy than for the MC-induced one (6 vs. 53; $p << 0.001$), and therefore, the frequency of seizures also differed significantly (pTh: 1.9/h; pTh/MC: 24.5/h; $p < 0.01$). Only the seizure frequencies of the pTh and the pTh/MC rats were significantly correlated ($r = 0.77$; $p < 0.01$) (Table 1). This correlation makes it likely that the sensitivity for the induction of seizures is a basic character of the individual rat, while the sensitivity for the maintenance of epileptiform activity is a specific character of the focus site.

The time course of the seizure frequencies for both the pTh and the pTh/MC rats differed in dynamics during the early period of epileptiform activation. Although the absolute seizure number was lower in pTh rats than in pTh/MC rats, their relative peak seizure frequency occurred 30 min after PCN injection and decreased thereafter markedly. This decrease correlated with the period when large potentials develop. In contrast, pTh/MC rats increased their seizure frequency until 90 min after epilepsy induction and decreased it gradually thereafter (Fig. 10, left). Interestingly, the last seizure during pTh and pTh/MC epilepsy developed at about the same time (146 min vs. 165 min, respectively) (cf. Table 1), even for the two rats with maximum duration of ictal activation (298 min vs. 325 min).

In the pTh rats, the development of large potentials exerted a significant influence on the interictal activity as well as on the frequency of generalized seizures. During the period of large interictal potentials, phases with superimposed sharp potentials were short and covered a median length of 11.6% (min 0%; max 42.9%) of time with respect of the total period with large potentials (cf. Fig. 5). This indicates that large potentials may suppress the development of sharp potentials. In 6

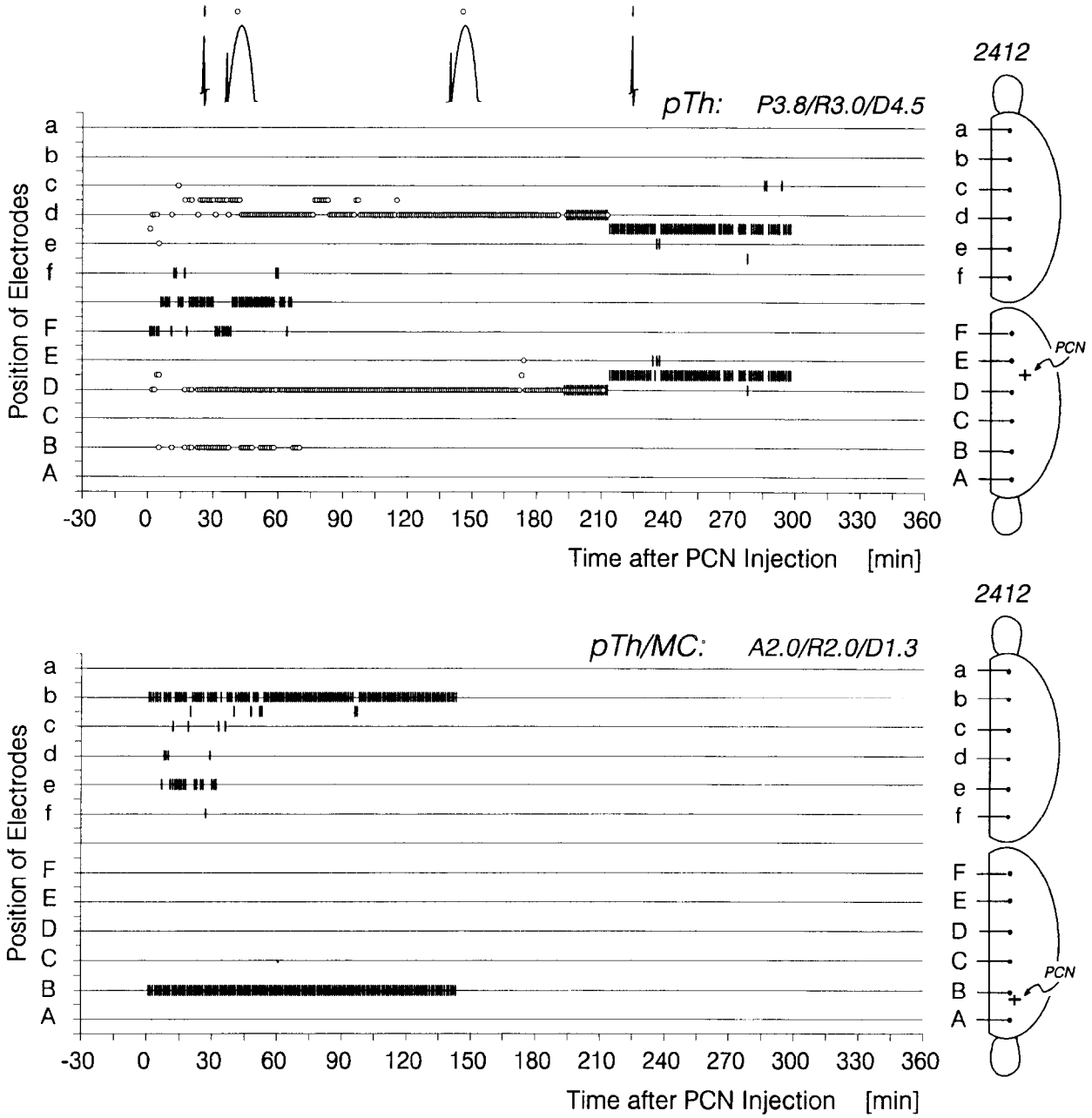

FIG. 7. Time courses of the cortical focal pattern of interictal activity induced by a PCN focus within the right posterior thalamus (pTh) or right motor cortex (MC). A representative rat (rat 2412, cf. Fig. 4) that was treated first in the right pTh (upper plot), and 2 weeks later in the right MC (pTh/MC) (lower plot) at the stereotaxic coordinates indicated on the upper right side of each plot. Horizontal lines, sites of the recording electrodes over the right (A–F) and left (a–f) hemispheres. Circles and bars on these lines, sites of characteristic focal activation within the corresponding minute for the large (circles) and the sharp (bars) potentials. pTh-treatment (cf. upper plot): Note the predominant activation of the occipital cortex (electrodes F, f) by the sharp potentials during the first 75 min after PCN injection, and the development of bilateral foci at the transition area between the sensory cortex and the motor cortex (electrodes D, d) for the large potentials. pTh/MC-treatment (cf. lower plot): Note the predominent development of the mirror focus near the electrode b with respect to the primary one located at electrode B.

out of 10 rats, the severity of interictal activity was analyzed for the transition from the period with an exclusive development of large potentials to the subsequent period with sharp potentials only (Fig. 9). It was found that the interictal frequencies significantly increased during this period in each rat, although the focal representations of both potential types in the cortex were close together (cf. Fig. 8, upper right and lower left). This increase in frequency was closely linked to the disappearence of the wave component of the large potentials.

The seizure frequency recorded for periods with large po-

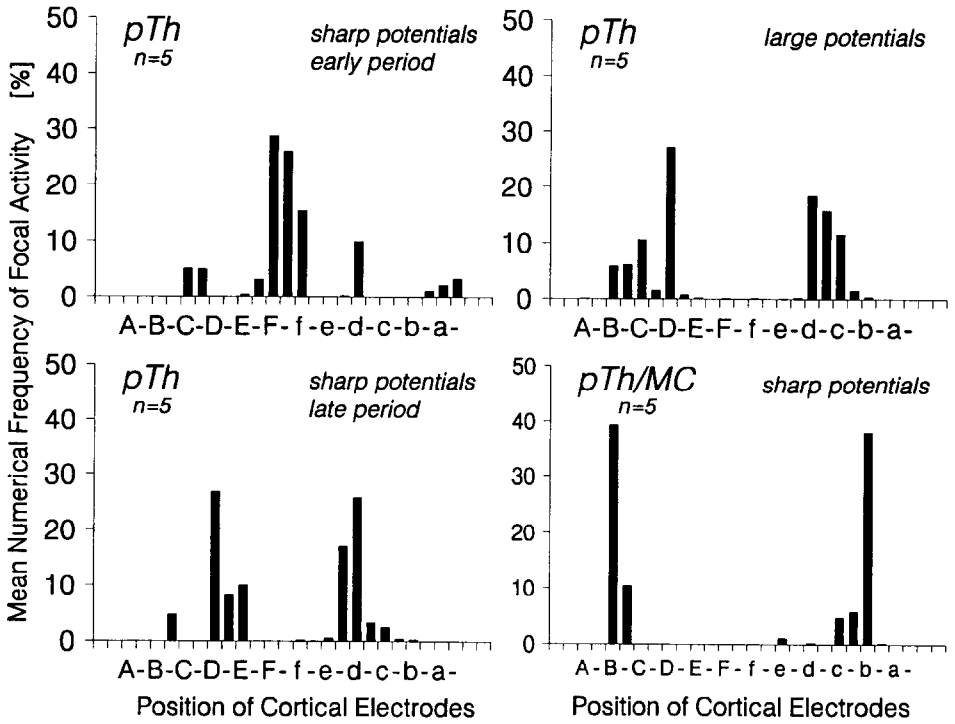

FIG. 8. Probability for the occurrence of focal interictal activity induced by a PCN focus within the posterior thalamus (pTh) or the right motor cortex (MC) 2 weeks later. Upper plots and lower left plot: probability distribution of focal activation after local injection of PCN into the right pTh. The early, middle, and late periods are shown in separate plots. Lower right plot: same animals after injection of PCN into the right MC (pTh/MC-treatment). Columns at F/f (A/a) indicate the occurrence of a focal activation that may randomly shift between the most occipital (frontal) right and left hemisphere. A–F, a–f, location of the electrodes (see also Fig. 1). n = 5 rats.

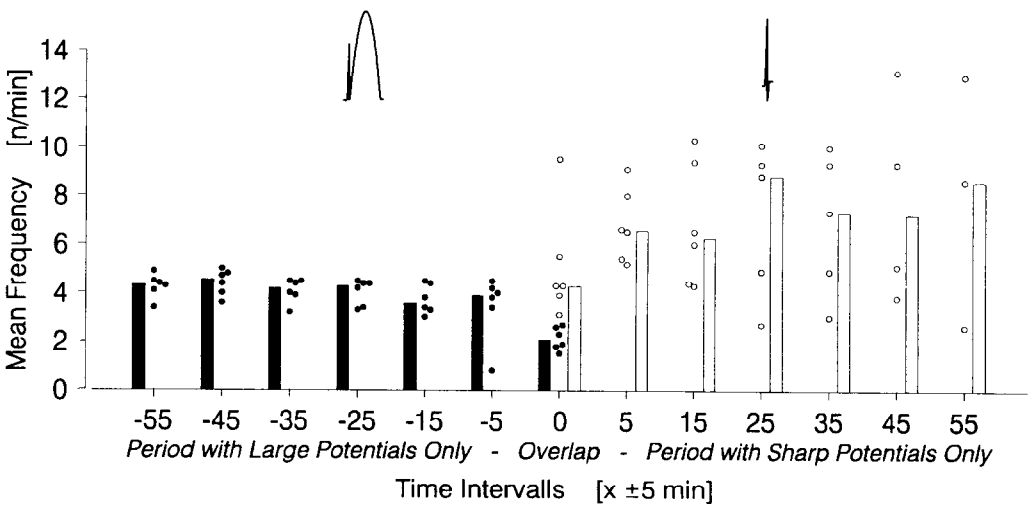

FIG. 9. Time course of interictal activation before and after disappearence of the large potentials. Frequencies (potentials per min) were calculated for 10 min lasting intervals (× ± 5 min). The time interval zero was taken from the period with simultaneous occurrence of large and sharp potentials (= overlap). Black and white columns, median frequencies for large and sharp potentials, respectively. Dots and circles, frequency values for large and sharp potentials, respectively, of individual rats. n = 6 rats.

TABLE 2

NUMBER OF SEIZURES PER HOUR IN RELATION TO THE FREQUENCY RANGE OF INTERICTAL ACTIVITY

	Frequency Range of Interictal Activity			
Rat No.	< 7/min Total Period	< 7/min 60 min After Onset	< 8/min	< 16/min
2410	0.9	2	1.0	0.9
2411	0.0	0	0.9	1.6
2412	0.5	0	1.6	—
2431	1.0	1	1.9	—
2432	0.2	1	2.7	3.2
2433	0.7	1	7.5	—
2434	0.0	0	3.3	3.3
2437	0.3	1	0.1	—
2439	0.2	0	10.0	12.0
2446	0.4	1	2.4	4.3
Median	0.35	1	2.15*†	3.25†

Number of seizures per hour during the periods with characteristic frequencies of interictal (focal) activity. < 7/min, periods with exclusive occurrence of large potentials; > 8/min, periods with occurrence of sharp potentials only or overlapping periods with large potentials; 16–50/min, period with exclusive occurrence of sharp potentials above the mean frequency range of 16/min (cf. Fig. 5). The epileptiform activity was induced by a local injection of penicillin at a concentration of 125 IU PCN/0.25 μl 0.9% NaCl into the posterior nucleus of the thalamus. Values for the individual animals and the medians of the sample. Significance levels vs. < 7/min: *$p < 0.01$; †$p < 0.002$.

tentials only was also significantly reduced compared to those determined from periods with sharp potentials (Table 2). In particular, its median during the first hour of the period with large potentials was 1/h, and 0.35/h for the whole period. If all periods with sharp potentials at frequencies > 8/min were considered including the overlap periods with large potentials, the median seizure frequency was 2.15/h. During periods with sharp potentials only at frequencies > 16/min, the median seizure frequency was 3.25/h.

In 5 out of 10 pTh rats it was possible to calculate the number of seizures before the first large potential developed for a period of at least 20 min with a time resolution of 10 min. After cumulation of these data, the resulting histogram showed a clear drop down of the seizure number immediately when the large potentials appeared (Fig. 10, right).

DISCUSSION

A few number of investigators have considered the contribution of the posterior thalamic nuclei to epilepsy. In artificially ventilated rats, an epicortical PCN focus led to a higher uptake of glucose, especially within the posterior thalamus compared to the venterolateral, venteropostero-lateralis or -medialis areas (5). Increase of GABAergic transmission by a local injection of muscimol into the posterior nuclei suppressed generalized convulsive seizures in the spontaneously epileptic Mongolian gerbil (21); a bilateral elimination of this area by a surgical lesion, however, did not affect the generalized, nonconvulsive absence (spike-and-wave) epilepsy in rats (35). The pulvinar-lateralis posterior nucleus complex of cats, which can be considered as a part of the posterior thalamic nuclei [cf. (25)], developed epileptic activity after a local injection of PCN (27).

The experiments dealt with here are another example of the epileptogenic properties of this thalamic area that become visible after a disturbance of the inhibitory GABAergic system. The PCN-induced focal activity pattern was characterized by two different types of potentials that differed in shape (Fig. 3), mean discharge frequencies (Fig. 4; Table 1) and cortical representation (Fig. 8). Therefore, this pattern is completely different from that induced by a PCN focus within the motor cortex. The latter is characterized by only one potential type and a clear unilateral or bilateral activation in the homotopic areas with no significant focus shift [cf. also (16)]. A shift of the epileptic focus was described for a PCN focus located within the olfactory cortex, but as for the MC epilepsy, the shape of the focal potential remained constant throughout the epileptiform activation (16). In general, the investigation points to two interesting aspects, (a) the neuronal connectivity of the posterior thalamic complex with other cerebral areas during epileptiform activity; and (b) the negative correlation between the specific type of focal activation and the severity of interictal and ictal epileptiform activity (Figs. 9, 10; Table 2).

The Neuronal Connectivity of the Posterior Thalamic Complex During Epileptiform Activity

Generally, it is only speculative to identify specific pathways from a systemic approach. Nearly all cortical neurons receive direct thalamic input (38) even from neurons of the posterior group [cf. (10)]. However, some facts are of interest for the interpretation of the presented results. First of all, a selective activation of cortical areas by a local activation of the posterior thalamic area was demonstrated. These areas included the occipital (visual) cortex and the transition zone between the motor cortex and the sensory cortex (Fig. 8). Secondly, thalamic neurons located in the lateral nuclei operate under an intrinsic oscillatory mode. Brief episodes of repetitive depolarizations (8–12 Hz) and burst discharges recurred every 10 s. In the interval, the membrane potential of these neurons slowly hyperpolarizes (8). A similar rhythmicity was observed for reticular thalamic neurons in cats (29). It was shown by these authors that the slow repetition rate was an intrinsic property of the thalamus. Finally, the mean discharge frequency for the large potentials (Fig. 4; Table 1), recorded by the cortical EEG showed low frequency values between 1 and 11/min (cf. also Table 1 for the range of the mean frequencies); this frequency range was similar to that recorded from the neurons within the lateral and reticular thalamic nuclei (8,29). It is, therefore, likely that the large potentials are the expression of a specific activity of the lateral and/or reticular thalamic nuclei complex.

Based on this conclusion, the hypothesis is that during the early period after the intrathalamic PCN injection a set of neurons in the occipital cortical area is activated by the efferent output of the posterior thalamus. These neurons may trigger those lateral and/or reticular thalamic neurons that have a high potential for self-sustained synchronization. The existence of cortical neurons that trigger thalamic neurons into self-sustained activity has been demonstrated by simultaneous recordings from cortical and thalamic neurons during spike-wave discharges induced by systemic administration of PCN (3). The self-sustained thalamic activity, which, in some instances may develop slowly (cf. Fig. 5), activates cortical areas located at the overlapping zone between the sensory and the motor cortex (cf. Fig. 8). According to this hypothesis, the posterior thalamic area influences the epileptic activity mainly during the first hour, while later the cortically recorded activity is maintained by a self-sustained activation of lateral or reticu-

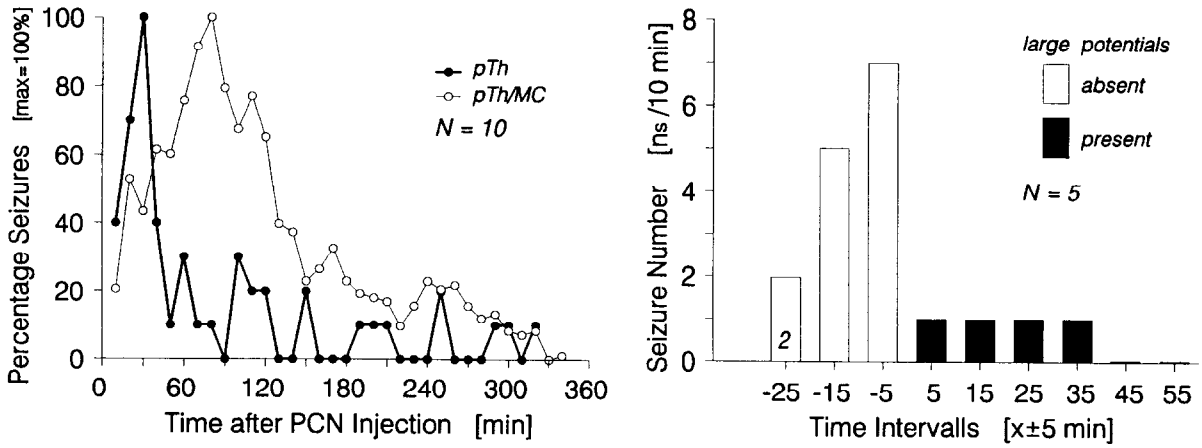

FIG. 10. Time courses of seizure numbers during epileptiform activity induced by a PCN focus within the posterior thalamus (pTh) and the right motor cortex 2 weeks later (pTh/MC). Left: normalized time courses of seizure numbers for the pTh and the pTh/MC rats (dots/fat line and circles/thin line, respectively). 100% = maximal seizure number during a 10 min lasting intervall for the pTh rats and pTh/MC rats, respectively. n = 10 rats. Note the marked decrease of the relative seizure number in the pTh-rats, 30 min after PCN injection; at this time the pTh/MC rats still increased their seizure number. Right: Cumulated number of seizures in pTh rats for at least 20 min before (white columns) and for 60 min after (black columns) the first appearence of large potentials which happened at time zero. Only data from the rats 2411, 2432, 2433, 2439, and 2446 (cf. Fig. 5) could be used. In both the left and the right figure, the number of seizures (ns) were counted for 10 min lasting intervals.

lar thalamic neurons due to their high intrinsic potential for synchonization of self-sustained activity.

Antiepileptic Effect of Repetative Thalamic Activity

Beside their epileptogenic properties (9,12,24,27,36,39), thalamic areas are also able to reduce epileptiform activity if they were stimulated electrically. In humans, electrical stimulation of the centromedial, anterior or reticular nuclei reduced different typs of epilepsy (1,2,33,34). In cats, epileptiform activity induced by local application of PCN in the visual cortex or the motor cortex was suppressed by electrostimulation of the mediocentral, lateral geniculate, or ventrolateral thalamic nuclei (20,36).

The present investigation demonstrates that generalized (Fig. 10, right; Table 2) as well as focal (Fig. 9) activity were reduced or even suppressed during the period of the large, wave-like or spike-wave-like potentials. In the spike-wave complexes of absence-like epileptiform activity, the spike expresses excitatory processes while the wave correlates with inhibition (3). We found that the disappearence of the wave is accompanied by an increase of the interictal frequency (Fig. 9). It is, therefore, likely that periods with large potentials during epileptiform activity originating from a PCN focus within the posterior thalamus are characterized by augmented inhibition. This postulation corresponds to the observations of a prolonged slowly developing hyperpolarization during the period between burst discharges of reticular and lateral thalamic neurons (8). Both observations point to intrinsic inhibitory thalamic activities that may have antiepileptic properties. A negative correlation between the occurrence of epileptic spikes and specific cerebral activation was also observed for an intrahippocampal PCN focus. During the period of hippocampal theta activity, induced by stroking the fur, the frequency of interictal hippocampal activity was reduced (22).

In contrast to electrical stimulation, the proposed antiepileptic action of the wave component, typical for large potentials in pTh rats, is based on a pathophysiological mechanism; thus, it is of endogenous origin. Therefore, thalamic areas may be involved in the formation of autoprotective mechanisms [cf. (15,17–19)], which protect the brain against excessive hyperexcitation. This tantilizing suggestion needs further experiments for verification.

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