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Protective Sensitivity Changes of the Motor Cortex Due to Epileptiform Experience of the Visual Cortex

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HORN, E., K. ESSELING AND R. WEBER. *Protective sensitivity changes of the motor cortex due to epileptiform experience of the visual cortex.* PHARMACOL BIOCHEM BEHAV **44**(3) 709–715, 1993.—In awake rats, experiments were performed to study early epileptiform events (interictal spike, myoclonic jerk) in relation to a) the strength of the convulsive stimulus, b) the site of the focus, and c) epileptiform experience. For this reason, Na-penicillin G (PCN) was injected either into the motor or visual cortex and, in a second test 2 weeks thereafter, into the motor cortex in all these rats. The median latencies of both the first interictal potential and jerk were independent of the applied PCN concentration in the range between 16–1,000 IU/0.5 μl (90.5–113 s, and from 106–196 s, respectively), as well as from the injection site in the visual or motor cortex (potential: 80 vs. 69 s; jerk: 124 vs. 129 s, respectively). After epileptiform experience in the visual cortex, the latencies of the first potential and jerk were significantly ($p < 0.05$) increased compared to animals with an experience in the motor cortex (first potential: 100 vs. 66 s; first jerk: 159 vs. 116 s, respectively). The results show that a PCN focus in the visual cortex decreases the susceptibility of the motor cortex for the convulsant action of PCN. This means that an autoprotective mechanism is activated whose efficiency depends upon a close linkage between the visual and motor cortex.

Anticonvulsant mechanism Interictal activity Rat Penicillin Motor cortex Visual cortex Sensitivity

EXPERIMENTAL models and human epilepsy research have shown that epileptiform activity causes cell damage including degeneration of neurons, gliosis, and dendritic spine loss (17). Focal models of epilepsy revealed cell damage especially if epileptiform activity was induced by agonists of the excitatory neurotransmitter glutamate like kainic acid (1,21). Similar massive neurotoxic effects are unknown for epileptiform activity induced by disturbances of the cerebral GABAergic system (17). In particular, intrahippocampal GABA injections caused acute glial swelling but no other neurotoxic effects (20). Bicuculline, a GABA antagonist with convulsant properties (3), did not display severe cell damages except swelling of dendrites and astrocytes (20). For penicillin (PCN), a GABA antagonist widely used to elicit focal epileptiform activity [cf. (16)], residual anatomic damage following a single convulsion induction is unknown so far. On the other hand, reduced GABA synthesis, concentration, and uptake were described in a PCN focus (6), demonstrating the pathophysiological defects in this focus. It can be supposed, therefore, that even these slight defects cause sensitivity changes of the brain. From the functional point of view, the mirror or secondary focus (13,14) and the kindling phenomenon (5) are important examples of long-lasting sensitivity changes of brain areas.

Experiments were performed to study in rats with epileptiform experience whether residual effects can be demonstrated by means of physiological methods. In the awake rat, PCN-induced epileptiform activity is composed of trains of interictal (epileptiform) potentials and myoclonic movements of the legs or the head (jerks) that are from time to time interrupted by secondarily generalized seizures [cf. (7)]. Therefore, the crucial experiment for the above-mentioned purpose was to determine the onset of events characteristic for the early period of the PCN-induced epileptiform activity in animals with epileptiform experience, that is, to record the latencies of the first epileptiform potential and myoclonus. It is likely that under these conditions developing sensitivity changes within the cerebral GABA system will become evident.

METHOD

Experiments were performed with 111 awake male and female Wistar rats (5–8 months old) from the stock of the Centre for Experimental Animals of the University of Ulm (FRG). Animals were kept under a 12 L : 12 D cycle. Under pentobarbital anesthesia (Nembutal; 65–75 mg/kg body weight, IP), one or two guiding tubes used for the local PCN treatment and 6 AgAgCl electrodes to record the cortical activity [electroencephalograph (EEG)] were fastened to the skull 0.3 mm

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above the dura. The stereotaxic coordinates of the electrodes were A4.5 and R/L1.8, P1 and R/L2.3, and P5.8 and R/L2.7 (with respect to bregma). After this preparatory operation, animals were housed individually and handled daily for at least 5 min until the convulsion tests were performed.

Convulsive activity was induced by a local application of 0.5 μl of a Na-penicillin G solution (PCN) into the cortex at a depth of 0.8 mm. In a group of 81 male and female rats, PCN or its solvent was injected into the motor cortex at the stereotaxic coordinates A2 (bregma) and R2. This group was used to investigate dose relationships. Seven PCN concentrations were used, the lowest being 16 IU/0.5 μl and the highest 1,000 IU/0.5 μl sterile 0.9% NaCl solution. In a second group consisting of 30 female rats, two injections were performed in each animal. The sites of the first injection were located either in the right motor cortex at the stereotaxic coordinates A4.5, A2 or A1 and R2 or in the visual cortex at P5.5 or P7.5 and R2.5. In all these 30 rats, the second injection was performed at the coordinates A2 and R2 14 days after the first one. The concentration of the injected PCN solution was 125 IU PCN/0.5 μl.

During the EEG recordings, rats could move freely in a chamber of 25 × 25 × 40 cm^3. An experiment usually started with a control recording lasting 1 h. In no case could any convulsive activity be recorded during this period. For injection, animals were disconnected from the EEG recorder. The application was performed without anesthetization while the carefully handled rat was kept in the hand of the experi-

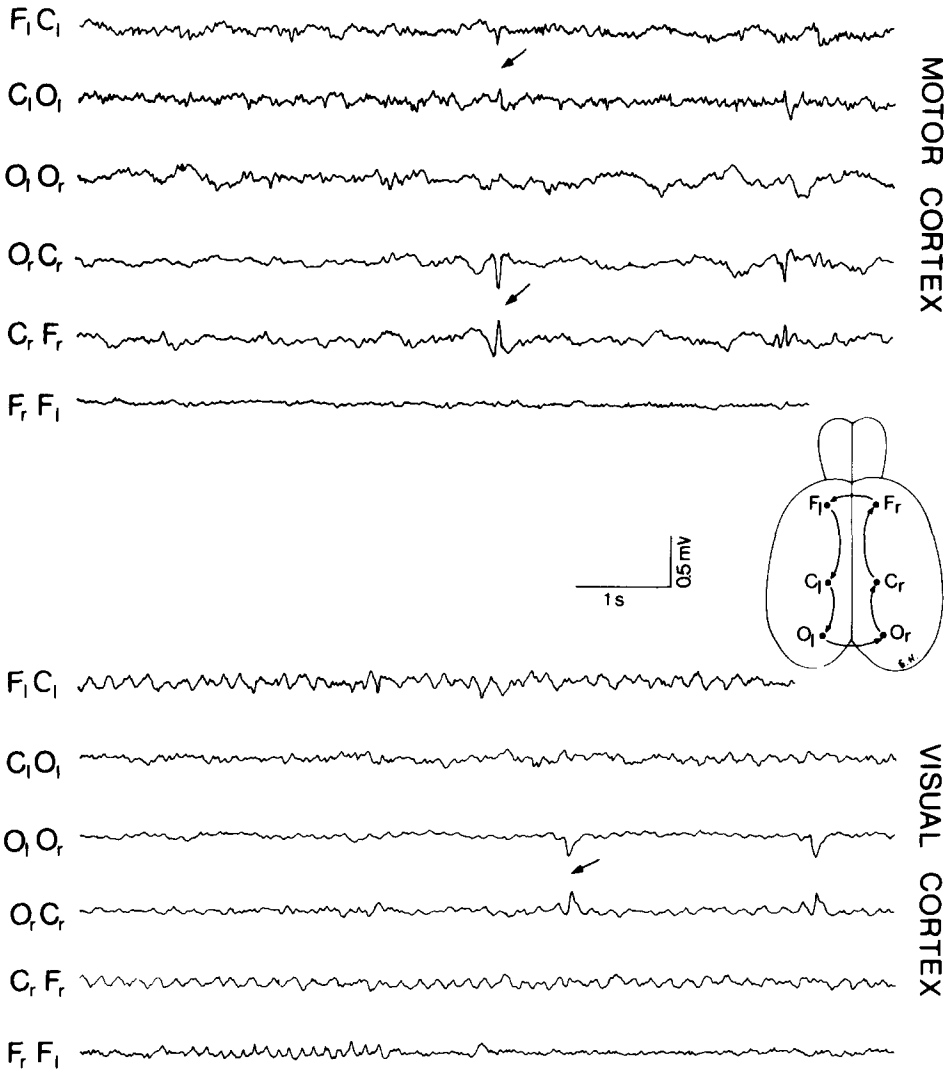

FIG. 1. Two examples showing the first epileptiform potentials elicited by a local injection of penicillin (PCN) into the motor [upper electroencephalogaph (EEG)] or visual (lower EEG) cortex of the right hemisphere in two awake rats. On the left margin, the type of the differential recording is indicated, with F, C, and O representing the frontal, central, and occipital electrodes, respectively, and l and r the left and right sides, respectively. Note the height of the potentials on the traces C_rF_r and O_rC_r in the case of the PCN focus in the motor or visual cortex, respectively. The first potentials are marked by arrows; the upper two traces give an impression for the critical size of a potential to be defined to be the first.

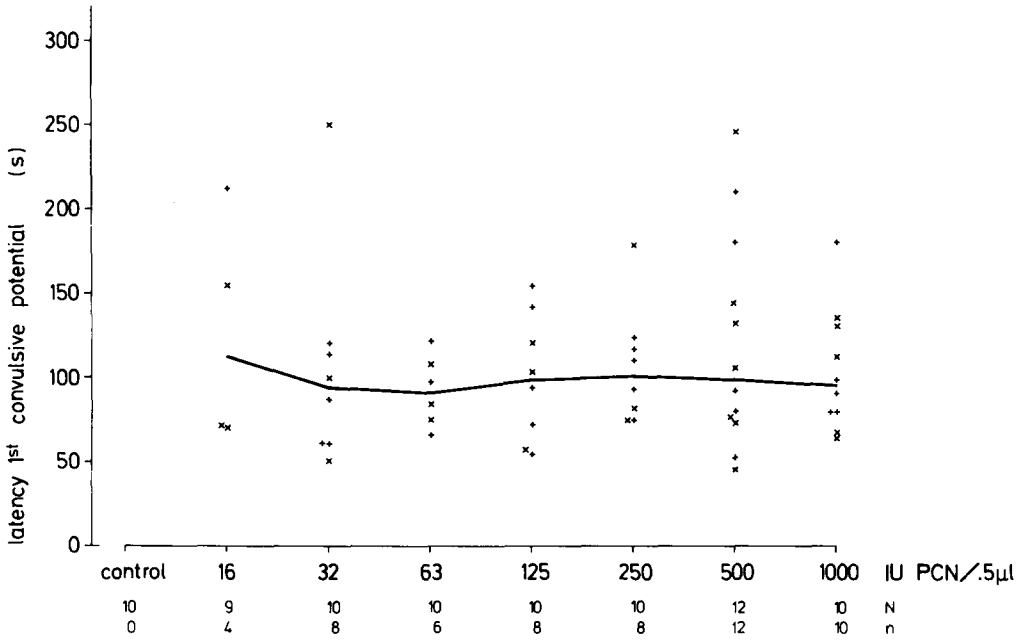

FIG. 2. Latency for the first convulsive potential in relation of the concentration of penicillin (PCN) injected into the motor foreleg area of the right hemisphere in awake rats. The thick line connects the median values obtained from the male (x) and female (+) rats for the corresponding dose. N = number of rats tested; n = number of rats from which convulsive potentials could be recorded.

menter. After injection of PCN, animals were immediately connected to the EEG recorder. The lack of recording time after injection was less than 30 s, considerably shorter than the latency of the first convulsive potential. Animals were sacrificed at the end of the experiment. Brains were sectioned and stained with cresyl violet to determine injection sites. In no case were the corpus callosum or other subcortical brain structures injured as demonstrated by the location of the lowermost point of injection tract.

The first potential was determined from the EEG recording. A potential was considered to be the first if in the vicinity of the focus its amplitude was larger than three times the base line fluctuation of the EEG (Fig. 1). The first jerk movement was recorded by a careful visual observation of the animal. In addition, the mean frequency of potentials (n_p/min) during the first 10 min was determined from the EEG recording. For statistics, the nonparametric U-test from Wilcoxon, Mann, and Whitney (27) was used. In the figures, individual and median values are given. If not included in the figures, p-values are given in the text.

RESULTS

Latencies of Early Epileptiform Events in Relation to the Injected PCN Concentration

The early period of convulsive activity was investigated in a group of 71 male and female rats for different PCN concentrations ranging from 16–1,000 IU/0.5 µl. The PCN solution was only injected into the motor cortex. Neither the latency of the first epileptiform potential (Fig. 2) nor the latency for the first jerk (Table 1) were significantly affected by the applied dose. In particular, the median values for the first potential ranged from 90.5–113 s and that for the first jerk from 106–196 s. The longest latency value for the first jerk was obtained after injection of the lowest concentration but due to the large interindividual variability of the values (cf. Fig. 2) the difference to the other experimental groups was insignificant ($p > 0.1$) except for the 32-IU group ($p = 0.01$).

A slight increase was observed for the initial frequency of the potentials only in the low-dose range. In particular, for the lowest PCN concentration (16 IU/0.5 µl) the median frequency was 13.7 n_p/min, which differed significantly only from the median values recorded for the concentrations ≥125 IU/0.5 µl ($p < 0.05$). For the range of concentrations ≥32 IU/0.5 µl, the median interictal frequency increased insignificantly ($p > 0.1$) from 22.5 to 31.9 n_p/min. These results indicate that the initial period of interictal activity is independent of the applied dose of PCN (Table 1).

Control experiments (n = 10 rats) in which only the solvent of PCN, a 0.9% solution of NaCl, was injected into the motor cortex showed that in no case was any sign of epileptiform activity elicited. After such an intracortical injection, only in some instances was a slight tremor of eye or facial muscles observed transiently.

Latencies of Early Epileptiform Events in Relation to the Site of the PCN Focus and Epileptiform Experience

These experiments were performed with 30 female rats. The injected concentration was 125 IU/0.5 µl. The median latency of the first interictal potential occurring after a local injection of PCN into the motor cortex was 80 s, while after PCN treatment of the visual cortex it amounted to 69 s. The interindividual variability was rather high; the difference of the medians was not significant ($p > 0.2$) (Fig. 3, columns on the left side).

TABLE 1

RELATION BETWEEN THE CONCENTRATION OF INTRACORTICALLY INJECTED PCN, THE LATENCY OF THE FIRST CONVULSIVE POTENTIAL AND MOTOR RESPONSE, AND THE INITIAL FREQUENCY OF POTENTIALS

Concentration of PCN (IU/0.5 μl)	n	Latency to First Potential (seconds)	Latency to First Jerk (seconds)	Initial Frequency (n_p/min)	n
1,000	10	95.0 ± 13.0	114.0 ± 15.0	31.9 ± 1.6	10
500	12	99.0 ± 20.5	144.5 ± 29.5	23.8 ± 5.4	12
250	10	101.0 ± 13.9	116.0 ± 24.6	25.2 ± 8.9	8*
125	10	98.5 ± 24.3	107.0 ± 30.2	27.7 ± 5.0	8*
63	10	90.5 ± 15.9	110.0 ± 196.2	25.7 ± 10.0	6
32	10	99.0 ± 17.0	106.0 ± 17.0	22.5 ± 5.1	8†
16	9	113.0 ± 41.0	196.0 ± 251.4‡	13.7 ± 3.2§	4
Solvent	10	–	–	–	0

The initial frequency was calculated for the period of 10 min after the first convulsive potential. Equal numbers of male and female rats. N, number of rats tested; n, number of rats from which the corresponding parameter was determined. Median values and SE of the median are given.

*n = 9 for initial frequency.

†n = 7 for first jerk.

§$p < 0.05$ (at least) with respect to ≥125-IU groups.

‡$p = 0.01$ only with respect to the 32-IU group.

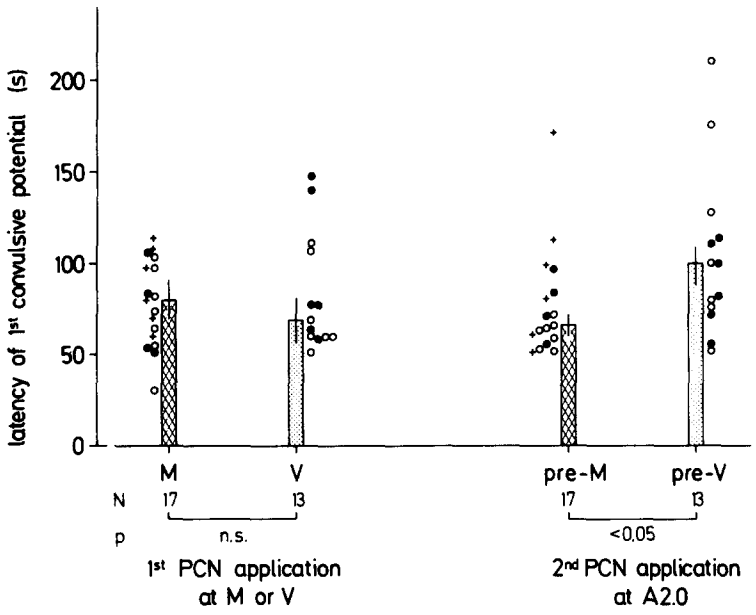

FIG. 3. Latency of the first interictal potential induced in awake rats by a local treatment of the motor or visual cortex with penicillin (PCN) (left two columns) and induced in the same animals by a local PCN treatment of the motor cortex at A2 2 weeks after the first treatment (right two columns). preM, preV, rats pretreated in the motor or visual cortex, respectively. Columns present the median value and its SE. Symbols on the left or right side of each column gives the value of individual animals. Injection sites in the motor cortex (M): ○, A4.5; +, A2; ●, A1. Injection sites in the visual cortex (V): ●, P5.5; ○, P7.5. All coordinates with respect to bregma. N = number of animals; p = level of significance; n.s. = not significant ($p > 0.1$).

The latencies of the first jerk for both the motor and visual cortex groups were similar, too. Their median values amounted to 124.0 and 129.0 s, respectively. Even the median frequency of the interictal potentials during the initial period, that is, during the 10-min period immediately after PCN treatment of the visual and motor cortex, were at the same level. For the visual group, it amounted to 32.7/min while for the motor cortex group a median frequency of 33.9/min was recorded (Table 2, upper part). This means that the latencies of early epileptiform events are not only independent of the applied PCN dose but also of the site of the intracortical PCN injection.

Two weeks after the first injection, the same animals were treated again with PCN, but in each animal the PCN injection site was located within the motor cortex at the stereotaxic coordinates A2 (bregma) and R2. The results obtained revealed some significant differences between rats pretreated in the motor or visual cortex. In particular, the median latency of the first interictal potential was significantly shorter in rats pretreated in the motor cortex than that of the group pretreated in the visual cortex (66 vs. 100 s, respectively; $p < 0.05$, U-test) (Fig. 3, columns on the right side). The same held if the median latency for the first jerk was considered (116 vs. 159 s, respectively; $p < 0.02$). The median initial repetition rate of the interictal potentials, however, did not differ significantly, although there was a slightly lower median value in the group pretreated with PCN in the visual cortex compared to that of the premotor group (25.5 vs. 37.3/min, respectively; $p < 0.1$) (Table 2).

It may be possible that the retardation for the occurrence of the first interictal activity in the visual group was caused by the longer duration of epileptiform activity during the first experiment. In fact, the median duration of interictal activity induced by a PCN focus within the visual cortex was 426 min; in rats with a PCN focus within the motor cortex, however, it was only 143 min. This difference was significant (U-test: $p < 0.05$). To test this possibility, the correlation coefficient r between the duration of epileptiform activity following the first PCN treatment and the latencies of the first interictal potential and jerk elicited after the second PCN injection 2 weeks later were calculated for both the motor and visual cortex groups. In no case was a significant correlation observed ($p > 0.1$). In particular, the correlation coefficients concerning the latencies of the first potential and jerk were $r = -0.21$ and $r = 0.25$ for the visual group and $r = -0.16$ and $r = -0.13$ for the motor cortex group (Fig. 4).

DISCUSSION

It is generally accepted that epileptic activity originating in a cerebral focus can change the sensitivity of brain tissue so that convulsive activity can be more easily exhibited. Examples are given by the kindling phenomenon, that is, the permanent alteration of brain function due to repeated local electrical or chemical stimulation (5,23). After major seizures have been kindled from one site, other sites within the brain also show greatly enhanced potential for triggering them (2) although sometimes with different time constants [cf. (18)]. In other experimental models, the formation of secondary or mirror foci (13) may also be due to sensitization of brain tissue as a result of repetitive activity of the primary focus [cf. (11)]. The time courses of their formation depends upon the location of the primary focus (9). This discovery indicated the existence of specific neuronal networks with different intrinsic properties concerning the induction and control of epileptiform activity caused by disturbances of the GABAergic cerebral system.

Contrary to a sensitization is a desensitization. In this case, cerebral structures became less sensitive against convulsant stimuli after former epileptiform experience. This observation was described for the site of primary kindling after secondary kindling of its contralateral, homotopic structure. It required several repetitions of daily stimulation of the primary site to overcome this anticonvulsant mechanism induced by the secondary kindling (12).

Our experiments present another example of a desensitization mechanism based upon a chemically induced epileptiform experience: A transient epileptiform activity originating from a PCN focus within the visual cortex increased the latency for the occurrence of the first interictal spike and myoclonic movement if PCN was injected into the motor cortex 2 weeks later while a primary PCN focus within the motor cortex did

TABLE 2

ONSET OF CONVULSIVE ACTIVITY IN RATS THAT RECEIVED 2 WEEKS AFTER A PCN INJECTION INTO THE MOTOR OR VISUAL CORTEX A SECOND INJECTION INTO THE MOTOR CORTEX

	First Potential (seconds)	First Jerk (seconds)	Initial Frequency (n_p/min)
Experiment 1: Injection in untreated rats into the			
Motor cortex ($n = 17$)	80.0 ± 11.0	124.0 ± 7.5	32.7 ± 4.3
Visual cortex ($n = 13$)	69.0 ± 13.6	129.0 ± 39.6	33.9 ± 3.5
Experiment 2: Injection at A2 in rats pretreated in the			
Motor cortex ($n = 17$)	66.0 ± 4.6	116.0 ± 11.3	37.3 ± 5.3
Visual cortex ($n = 13$)	100.0 ± 10.7*	159.0 ± 23.1†	25.5 ± 6.4‡

Experiment 1, first injection in the motor or visual cortex; Experiment 2, second injection into the motor cortex in all rats. The onset of convulsive activity is characterized by the latency of the first convulsive potential, the first motor response, and the mean potential frequency for the 10 min following the first convulsive potential. Median values and their SE are given. The table includes only those rats from which data from both experiments were recorded. N, number of rats.

*$p < 0.05$, †$p < 0.02$, ‡$p < 0.1$, respectively, compared with the motor cortex group in Experiment 2.

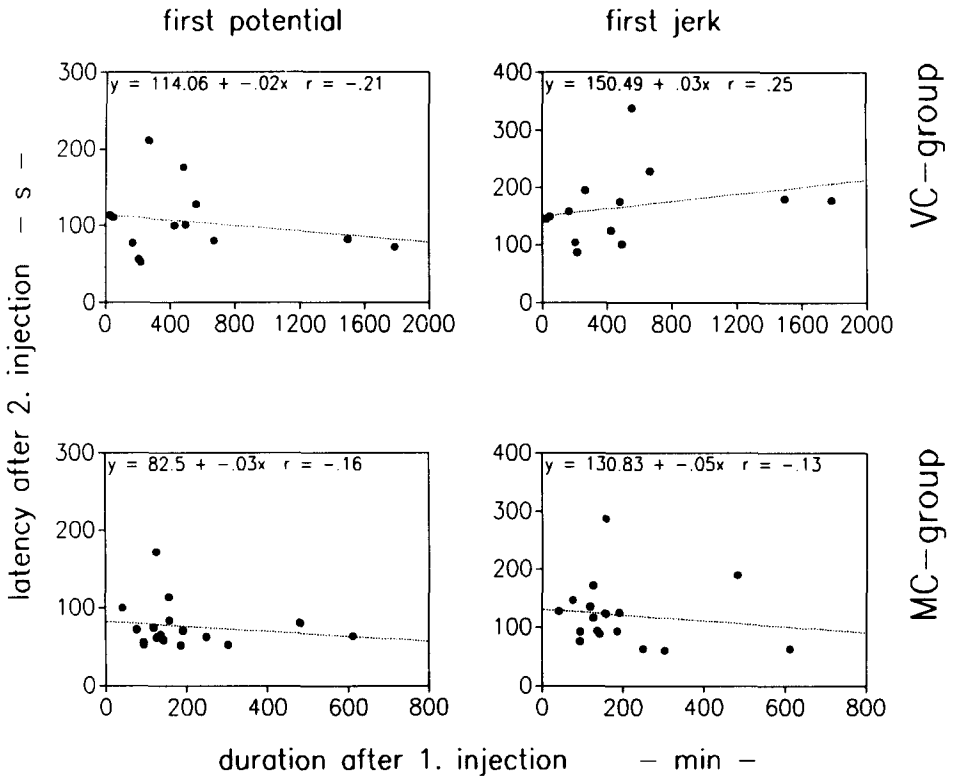

FIG. 4. Correlation diagrams in which the relations between the duration of the interictal activation period induced by a penicillin (PCN) injection into the visual or motor cortex (VC-group and MC-group, respectively), and the latency of the first interictal potential or jerk induced in the same rats by a PCN injection into the motor cortex 2 weeks later are presented. Note the low correlation coefficients r, which are in all cases insignificant. Same animals as in Fig. 3.

not exhibit this effect (Fig. 3). In general, the latency of early PCN-induced epileptiform events like the first interictal potential or the first motor response proved to be independent of the type of cortical stimulation (Fig. 2; Tables 1 and 2). This means that latency differences indicate differences of the animal populations. Rats taken from the same stock but differing in their latency values of the early epileptiform events should have taken a different history. This was precisely the condition of our experiments, in which residual effects of early epileptiform experience were investigated. Rats with epileptiform experience in the visual cortex possessed long-lasting residual effects (Fig. 3; Table 2), causing a decrease of the susceptibility of the motor cortex to the convulsant action of PCN. It is likely that rats have developed an intracerebral compensatory mechanism to protect their brain against further release of epileptiform events.

The ability of the brain to compensate for defects caused by lesions of sense organs is well known. One of the best-investigated examples is the "vestibular compensation," that is, the elimination of behavioral and neurophysiological defects caused by the destruction of one labyrinth (19). An epileptic focus is a cerebral defect (1,6,17,20,21), which probably activates compensatory mechanisms, too. In fact, they became evident from acute experiments in awake rats in which the relation between the locally injected dose of PCN and the duration of the epileptiform activity was investigated. For short-lasting activity induced by low PCN doses, the duration of interictal activity was mainly determined by the spread of PCN within the brain tissue due to diffusion. During long-lasting activity, however, the epileptiform activity terminated earlier than from the regularities of PCN diffusion could be expected. The underlying neuronal compensatory mechanism probably protects the brain against severe hyperexcitation but it needs some time to become operative (8).

Effective compensatory mechanisms were also derived from experiments based upon the paired-pulse depression technique in brain slices from kindled rats. Decreased (10) as well as increased efficiency of the second stimulus occurred (4,22), indicating a decreased or increased efficiency of the GABAergic recurrent system, respectively. The increased paired-pulse depression was still obvious 4 weeks after termination of the kindling procedure (4). Together with the effects of secondary kindling on the primary kindling site (12) and of a transient PCN focus within the visual cortex on the motor cortex (cf. Fig. 3), these observations point to the existence of cerebral "autoprotection" because a) the compensatory mechanisms were formed by the brain itself and b) their efficiency was long lasting. It may be that even in the normal brain autoprotective mechanisms are active at each time to overcome slight disturbances of the brain, but they cannot be detected. Autoprotective mechanisms can only be detected for visible defects like an experimentally induced epileptic focus.

It cannot be explained sufficiently why only rats with epileptiform experience in the visual cortex developed these long-lasting sensitivity changes of the GABAergic system within the motor cortex and why rats with epileptogenic experience

in the motor cortex did not. This problem has to be investigated in the future. One fact, however, should be stressed concerning the methodological view point. The present study as well as former observations [cf. (8)] revealed that after disappearance of PCN-induced epileptiform activity neither ictal nor interictal activity developed spontaneously during the following days. The detection of the supposed sensitivity changes of the motor cortex were coupled with a convulsant stimulus impinged on the cerebral tissue. It may be that without this strong stimulus the protective mechanism was efficient enough to overcome any spontaneous development of epileptiform activation.

In conclusion, this study shows that residual effects of a single PCN injection into the visual cortex leads to a significant decrease of the susceptibility of the motor cortex for the convulsant action of PCN. It is too early to draw any conclusion on the molecular basis of this decrease in brain sensitivity for the GABA antagonist PCN. But, this observation is a demonstration of the ability of the brain to form stable autoprotective mechanisms activated by epileptiform activity.

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