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Models of Simple Partial and Absence Seizures in Freely Moving Rats: Action of Ketamine

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VELÍŠEK, L., R. VONDŘIČKOVÁ AND P. MAREŠ. *Models of simple partial and absence seizures in freely moving rats: Action of ketamine.* PHARMACOL BIOCHEM BEHAV **45**(4) 889–896, 1993.—The action of ketamine was studied in two models of seizures: a) bilateral neocortical discharges produced by topical application of pentylenetetrazol (model of simple partial seizures); and b) rhythmic spike-and-wave activity induced by systemic administration of pentylenetetrazol (model of absence seizures). Ketamine exerted biphasic effects. In the first model, the dose of 20 mg/kg ketamine significantly suppressed the ictal neocortical discharges (i.e., continuous spiking or ictal activity) accompanied by clonic motor seizures. However, at the dose of 40 mg/kg ketamine significantly accentuated the onset and increased the number of individual discharges (interictal spikes) in bilateral neocortical foci. In the model of rhythmic spike-and-wave activity, the lower dose of ketamine (20 mg/kg) decreased the number of rhythmic spike-and-wave episodes when compared to the higher dose (40 mg/kg) of ketamine, which increased the number of episodes. However, neither result differed significantly from control values. The present results suggest a dose-dependent action of ketamine: Lower doses (10 and 20 mg/kg in the rat) are able to suppress seizure activity, whereas a higher dose (40 mg/kg) potentiates the seizures. Moreover, the action of ketamine may be dependent upon the seizure model used. The study presents a new model of acute epileptic focus in freely moving rats.

Neocortical focus Rhythmic activity Pentylenetetrazol Rat Ketamine

KETAMINE is a dissociative anesthetic that acts as an antagonist of NMDA-mediated transmission by blocking the phencyclidine (PCP) site at the NMDA–receptor complex (1,9,34). Earlier studies demonstrated that high concentrations of ketamine may act also on dopaminergic and noradrenergic (16), cholinergic (20), and serotonergic (35) systems. GABAergic transmission can be also affected by ketamine either directly or indirectly (38). These effects of ketamine appear to be dose dependent: Low doses of ketamine [2.5–20 mg/kg in the rat (1)] probably participate in NMDA–receptor blockade, whereas higher doses may involve other transmitter systems (16). These data suggest that the mode of ketamine action is dose dependent.

The effects of ketamine on seizures have been described in various models. Some studies found ketamine (5–40 mg/kg in rats) to be anticonvulsant against generalized tonic-clonic seizures induced by mercaptopropionic acid, pentylenetetrazol (PTZ), bicuculline, and picrotoxin (27,33,37,38). Other articles suggest that ketamine is proconvulsant because it activated epileptiform discharges in the neocortical cobalt focus or corticoreticular epilepsy [2.5–30 mg/kg in cats (3,12)]. This suggests that ketamine effects may be seizure model dependent: anticonvulsant in generalized seizures and convulsant in focal seizures, especially when focus is located in the neocortex. Both anticonvulsant and proconvulsant effects of ketamine have been reported in mentally retarded human epileptics [dosage 1–13 mg/kg (2)].

We used two substantially different models of seizures induced by PTZ to determine whether ketamine effects are dose dependent and seizure model dependent: a) Bilateral neocortical focal discharges induced by bilateral cortical application of PTZ (7) represented a model of simple *partial* seizures in freely moving rats. This model has been developed in our laboratory. b) Spike-and-wave rhythmic EEG activity was induced by systemic administration of PTZ (36). This may be a model of human absences (11,21,24,31), that is, primary *generalized* seizures.

METHOD

Animals

Sixteen male, adult Wistar, specific pathogen free, albino rats were used. Animals were housed individually with free access to food and water.

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Operation

Surgery was performed under pentobarbital anesthesia (50 mg/kg, IP). Two silver electrodes were placed in the visual cortex bilaterally (anteroposterior: 6 mm posterior to bregma; lateral 4 mm). Two other electrodes were placed in the sensorimotor cortex bilaterally (anteroposterior at the level of bregma, lateral 2 mm). In Experiment 1, the frontal silver electrodes were substituted by bilateral stainless steel guided cannulae (1.2 mm external diameter, length 20 mm, top angle 45°), which were used for the PTZ infusion and electroencephalograph (EEG) recording. These cannulae were inserted into the drilled holes in the skull (coordinates with respect to bregma: AP = 0 mm; L = ±2 mm) tightly on the surface of undamaged dura mater. The angle between cannula and skull surface was 45°, that is, the entire tip of the cannula lied on the surface of dura mater. An anchoring screw placed in the nasal bone served as the reference electrode. Both reference and active electrodes were attached to a female connector and the whole complex was covered with acrylic. Animals had at least 1 week to recuperate.

Drugs

Pentylenetetrazol (Sigma Chemical Co., St. Louis, MO) was diluted in distilled water. For topical application, the dilution was 200 mg/ml (pH = 7.6–7.7; osmolarity = 720 mOsm) and for IP administration 40 mg/ml (pH = 7.3–7.4; osmolarity 220 mOsm).

Ketamine (KET; Narcamon, Spofa, Czechoslovakia; 10, 20, or 40 mg/kg) was administered IP 10 min prior to administration of PTZ.

Topical PTZ

There were seven animals with implanted cannulae. Each animal was used four times with random distribution of non-pre-treated (NP) and KET sessions. The random distribution of the sessions was chosen to eliminate either the kindling effect of or developing tolerance to locally injected pentylenetetrazol. The interval between sessions was at least 3 days. In the NP group, 2 min of baseline EEG was recorded from frontal and occipital regions, bilaterally. Then, PTZ (2.5 μl) was applied into the each cannula using a Hamilton microsyringe (Hamilton Co., Reno, NV) over a period of 10 s. The length of the needle of the microsyringe was adjusted exactly to 20 mm, so the tip of the needle was not allowed to extend beyond the cannula boundary. EEG recording continued for 30 min. In KET-pretreated animals, baseline EEG was recorded for 2 min before KET administration, 2 min before PTZ application, and continuously for 30 min after PTZ application.

To assess the development and activity of bilateral neocortical focal discharges, we determined the latency to the onset of the first PTZ-induced spike and the number of interictal spikes in two arbitrarily selected 5-min intervals (within 5–10 min and within 15–20 min following PTZ application). The incidence and total duration of ictal activity (continuous spiking activity longer than 5 s) were also evaluated.

Intraperitoneal PTZ

Nine rats were used. As above, each animal was used four times, and the sessions were distributed randomly with at least 3-day intervals. The random distribution of experiments, although it probably increased the variances of data, eliminated the increased sensitivity of animals to the PTZ treatment. Repeated systemic subconvulsive doses of PTZ result in the manifestation of motor seizures [pharmacological kindling (13, 25,29)]. In the NP group, the EEG baseline was recorded for 2 min prior to PTZ administration. PTZ was injected in the dose of 40 mg/kg IP. This dose has been chosen for our breeding of Wistar rats because they displayed fast transition of response to PTZ between no manifestation and fully expressed motor seizures (unpublished data). The doses of 20–25 mg/kg PTZ used by other authors (11,24,31) had minimal EEG effects in our strain. EEG was continuously recorded for 30 min. In KET-pretreated animals, 2 min of EEG were recorded before KET administration, another 2 min before administration of PTZ, and continuously for 30 min thereafter.

We determined the latency to the onset of the first rhythmic pentylenetetrazol-induced activity, which started in occipital regions predominantly (36). The only clinical accompaniment was a motionless stare and vibrissae movements (39). The latency to the generalized rhythmic pentylenetetrazol activity (simultaneous onset in all four cortical regions recorded) was also determined. Moreover, we counted the number and total duration of rhythmic pentylenetetrazol activities within two arbitrarily selected intervals within a 30-min recording period (10–15 min and 20–25 min).

If the animal in this experiment displayed clonic seizures of facial muscles and forepaws, it was discarded from the experiment to maintain the features that are clinically closely similar to human absences (i.e., without apparent motor seizures).

Statistics

The data were evaluated using analysis of variance with posthoc comparison by Fisher's PLSD test [two tailed; (26)]. The incidence of ictal activity was compared using Fisher's exact test (18). The level of significance was set to 5%.

RESULTS

Topical PTZ

The baseline EEG consisted of fast activity with low amplitude in both NP and KET groups. Administration of 20 and 40 mg/kg KET produced rhythmic sharp waves or slow waves in all regions studied. The lowest dose of KET used (10 mg/kg) only increased the amount of high-frequency, low-amplitude activity. Symmetrical application of the PTZ solution upon the cortex elicited epileptic foci producing high-amplitude synchronous discharges (interictal spikes usually followed by a wave; Fig. 1A) associated with myoclonic body twitches, synchronous with the EEG discharges. The duration of the spike was shorter than 100 ms and the whole spike-and-wave complex did not exceed 500 ms. Ictal activity (continuous spiking for at least 5 s; $f > 2$ Hz; Fig. 1C) appeared as a late phenomenon with an average duration of 9–12 s and was accompanied by clonus of the forepaws and facial muscles. In the NP group, the latency of the first discharge was 40 ± 10 s (mean ± SEM). Administration of 10 and 20 mg/kg KET did not significantly change this latency. However, the dose of 40 mg/kg KET dramatically shortened the latency of the first discharge, $F(3, 21) = 2.95$, $p < 0.05$, in comparison with the NP and other KET groups (Fig. 2).

The total number of interictal spikes was counted at two intervals: 5–10 min and 15–20 min after PTZ administration. The number of discharges counted within the latter interval was lower than that counted within the former interval in

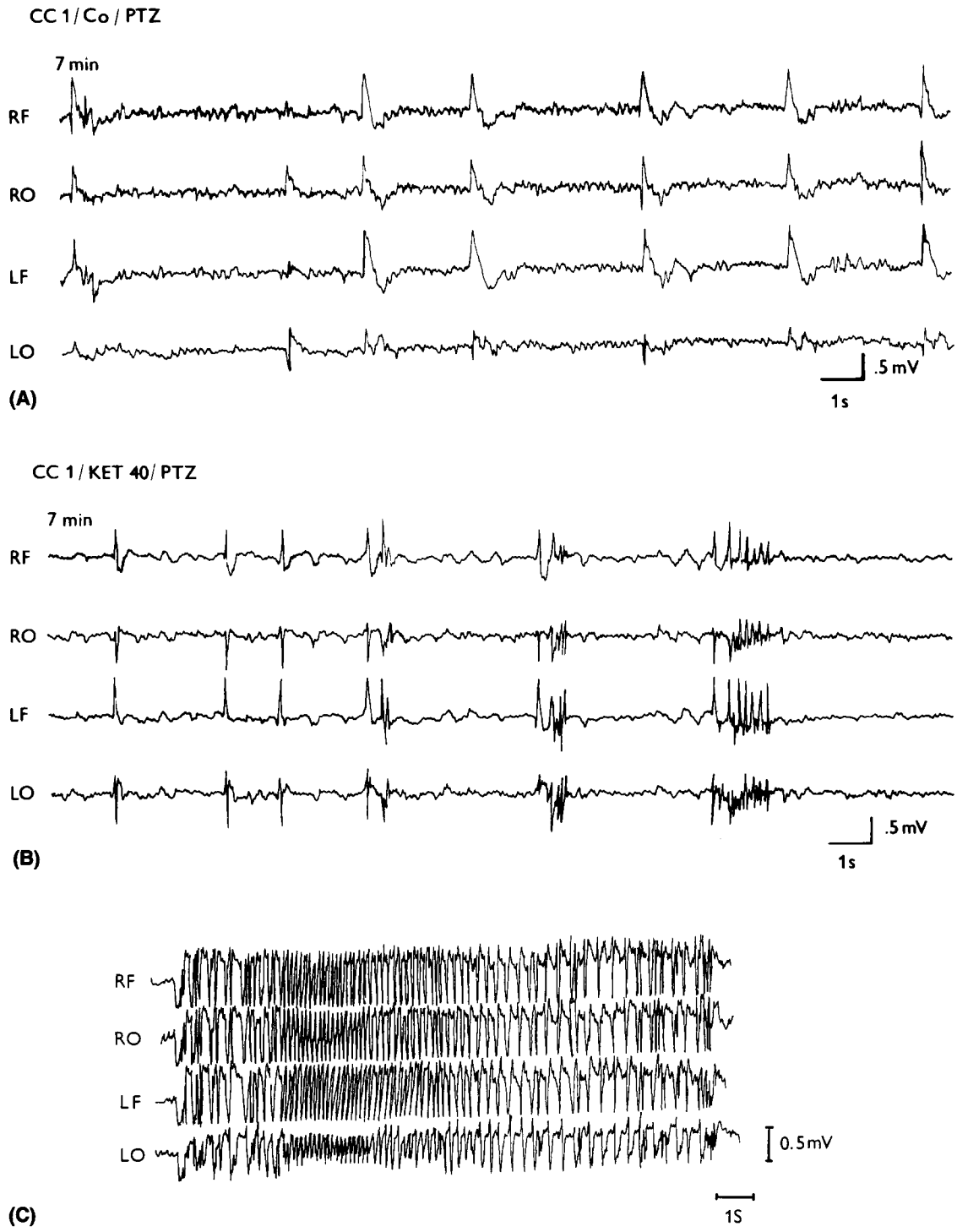

FIG. 1. Bilateral neocortical foci induced by pentylenetetrazol in freely moving rats RF, right frontal region; RO, right occipital region; LF, right frontal region; LO, left occipital region. All recordings are monopolar, that is, active vs. reference electrode inserted in the nasal bone. CC 1, animal with cortical electrodes no. 1. Calibration, 0.5 mV; time mark, 1 s. (A). Individual interictal focal discharges in an animal 7 min after local pentylenetetrazol application. (B). Interictal focal discharges formed by polyspikes in the same animal 7 min after pentylenetetrazol application but after pretreatment with 40 mg/kg ketamine 10 min prior to pentylenetetrazol. (C). Ictal activity in another animal formed by synchronous polyspikes and spike-and-wave discharges.

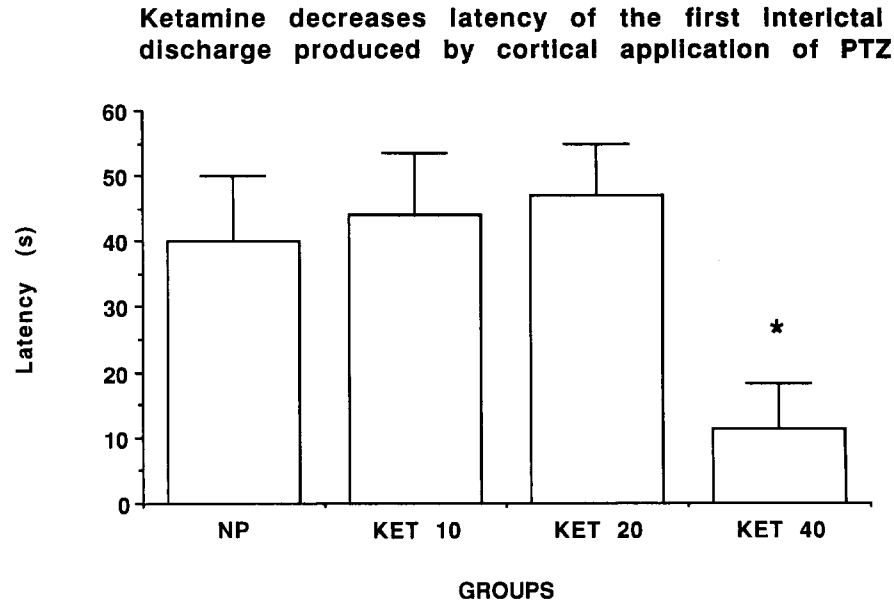

FIG. 2. Latency of the first interictal discharge (spike) in bilateral neocortical foci induced by pentylenetetrazol (mean ± SEM). Abscissa: Dose of ketamine in mg/kg; NP, received pentylenetetrazol only. Ordinate: Latency of the first interictal spike measured from the pentylenetetrazol administration in seconds. *Significant difference in comparison with the NP group (analysis of variance with posthoc Fisher PLSD test; $p < 0.05$). The dose of 40 mg/kg ketamine significantly shortened the latency to the first interictal discharge.

both NP and KET groups; however, the difference was not significant. In both intervals, KET caused a dose-dependent increase in the number of discharges. The dose of 40 mg/kg KET increased the number of spikes dramatically compared to both the NP group and the group pretreated with 10 mg/kg KET, $F(3, 21) = 3.35, p < 0.05$ (Fig. 3).

The incidence of ictal activity was also influenced by ketamine pretreatment. In the NP group, ictal activity was detected in 71.5% of rats. Pretreatment with 10 and 20 mg/kg KET decreased the incidence gradually to zero (Table 1). Administration of 40 mg/kg KET, however, increased the incidence of ictal activity back up to 60%. The total duration of

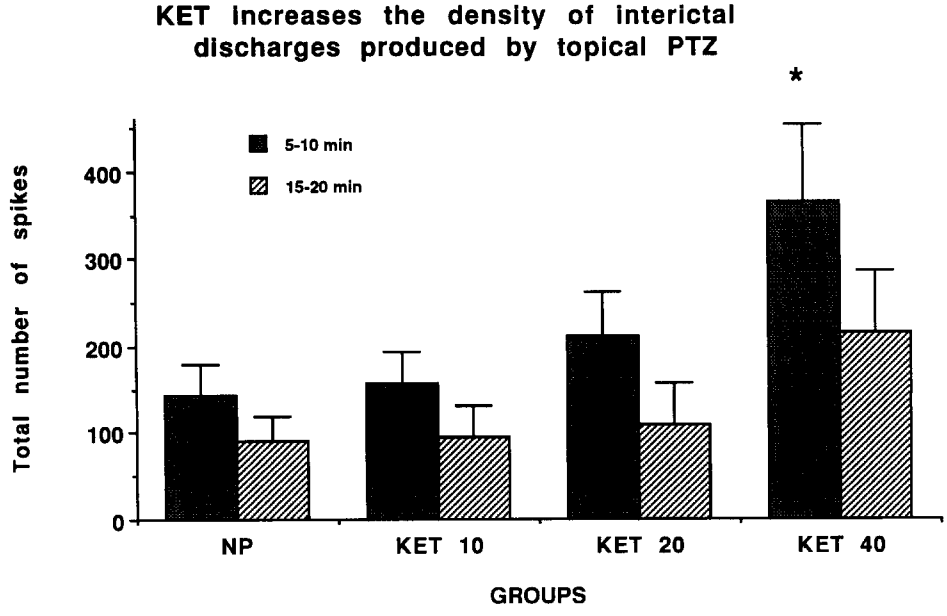

FIG. 3. Total number of individual interictal discharges (spikes) produced by bilateral neocortical foci induced by pentylenetetrazol within intervals 5–10 min and 15–20 min (mean ± SEM). Abscissa: See Fig. 2. Ordinate: Total number of interictal spikes. Pointed columns: Values for interval 5–10 min. Broken columns: Values for interval 15–20 min. For other details, see Fig. 2. The dose of 40 mg/kg ketamine significantly increased the number of discharges in the interval 5–10 min after administration of pentylenetetrazol.

TABLE 1

INCIDENCE OF ICTAL ACTIVITY INDUCED BY TOPICAL PENTYLENETETRAZOL

	Group			
		Ketamine (mg/kg)		
	NP	10	20	40
Incidence	71.5%	32.2%	0%*	60%

*Significantly different value from NP group (Fisher's exact test, $p < 0.05$).

the ictal activity did not differ between NP and KET-pretreated animals if there were sufficient data for the evaluation (Fig. 4).

Intraperitoneal PTZ

Administration of PTZ elicited episodes of rhythmic pentylenetetrazol activity initially in limited areas, predominantly occipitally (Fig. 5). However, the episodes progressed quickly to all areas recorded. During the episodes, animals interrupted their previous activity and became quiet, with a motionless stare. Only small rhythmic movements of vibrissae were observed. In the NP group, the latency to the onset of nongeneralized rhythmic pentylenetetrazol activity was 129 ± 13.5 s and to the onset of generalized rhythmic pentylenetetrazol activity 174 ± 43 s. Following administration of KET, the difference between the onset of nongeneralized and generalized rhythmic pentylenetetrazol activity was not so marked, that is, rhythmic pentylenetetrazol activity often began as generalized (the range of values for nongeneralized rhythmic pentylenetetrazol activity was 77–133 s and for generalized rhythmic pentylenetetrazol activity 80–135 s). Although the latency to the onset of rhythmic pentylenetetrazol activity decreased with the increasing dose of KET, this difference was not significant.

There were no differences between total number of rhythmic pentylenetetrazol activities in the 10- to 15-min and 20- to 25-min intervals in both NP and KET groups. In the NP group, the total number of rhythmic pentylenetetrazol activities within the first interval was 39 ± 7, whereas in the second interval it was 33 ± 5. A tendency to decrease the number of rhythmic pentylenetetrazol activities was seen following administration of 10 and 20 mg/kg KET. In contrast, the dose of 40 mg/kg KET completely reversed this trend [significant difference between 20 mg/kg vs. 40 mg/kg KET in the interval 10–15 min only; $F(3, 26) = 2.56, p < 0.05$].

The total duration of rhythmic pentylenetetrazol activity did not differ between the 10- to 15-min interval and the 20- to 25-min interval (69.4 ± 11 s and 69.7 ± 18 s, respectively) in the NP group. The KET pretreatments did not exert any significant changes.

DISCUSSION

Our study demonstrated that in the model of simple partial (focal) seizures produced by topically applied pentylenetetrazol doses of 10 and 20 mg/kg ketamine had no effects on individual discharges (interictal spikes), whereas the dose of 40 mg/kg significantly potentiated and accelerated the development of discharges in the foci. The 20-mg/kg dose of ketamine suppressed the ictal activity produced by the foci, yet no effect was exerted by the higher (40 mg/kg) dose of ketamine. In the model of absence (generalized) seizures induced by systemic pentylenetetrazol, doses of ketamine 10 and 20 mg/kg displayed only a nonsignificant anticonvulsant effect that was absent at the highest dose of ketamine used (40 mg/kg).

Ketamine has been found to be anticonvulsant in general-

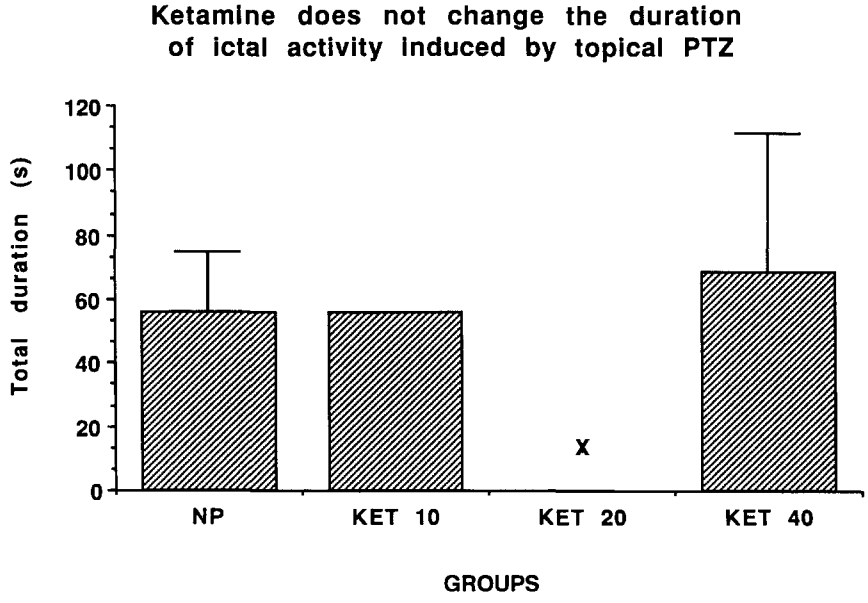

FIG. 4. Total duration of all periods of ictal activity produced by bilateral neocortical foci induced by pentylenetetrazol (mean ± SEM). Abscissa: See Fig. 2. Ordinate: Total duration of ictal activity in seconds. x: A phenomenon was not observed. Where the bar indicating SEM is absent, we did not have a sufficient amount of data for the statistics. There was no significant difference between the non-pre-treated (NP) and ketamine-pretreated groups.

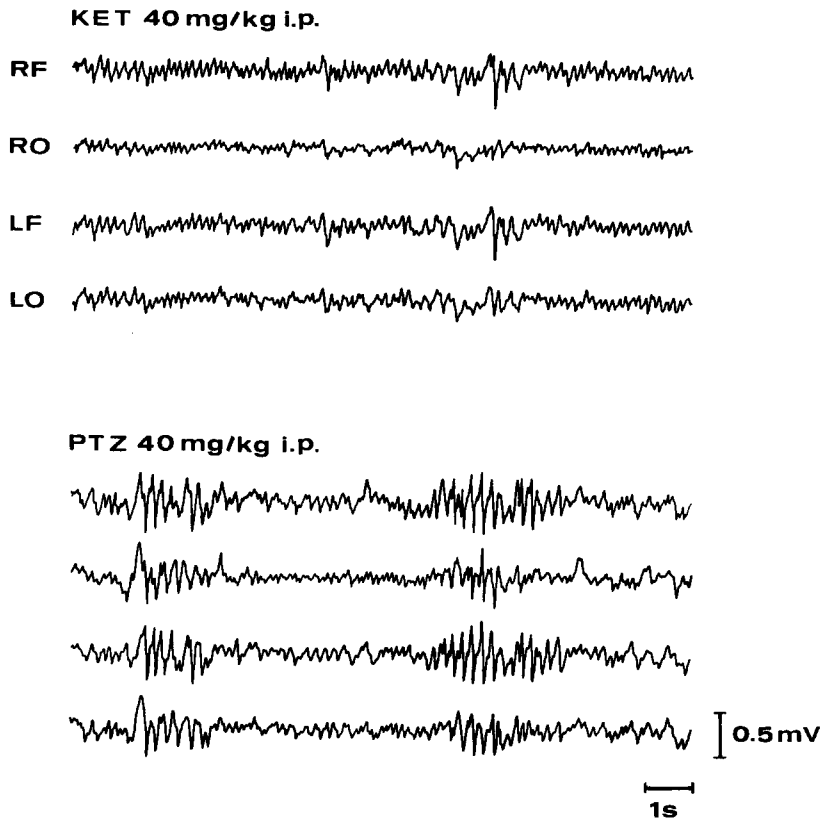

FIG. 5. Rhythmic pentylenetetrazol-induced activity in freely moving rat. Top: Baseline EEG after pretreatment with 40 mg/kg ketamine. Bottom: Two periods of rhythmic pentylenetetrazol-induced activity recorded in the same animal. Neocortical bipolar recordings (active electrode vs. reference electrode in the nasal bone). Active electrode regions: RF, LF, right and left frontal, respectively (with respect to bregma: AP = 0; lateral = ±2 mm); RO, LO, right and left occipital, respectively (AP = 6; lateral = ±4 mm). Calibration, 0.5 mV; time mark, 1 s.

ized seizure models (19,27,33). In our study, doses of 10 and 20 mg/kg ketamine suppressed the ictal activity produced by symmetrical pentylenetetrazol foci, which represents a higher level of generalization of epileptiform activity. There is evidence from microelectrode and microiontophoretic studies that ketamine acts as an NMDA antagonist (1,8). This conclusion is supported also by the ketamine-induced suppression of NMDA-induced seizures and lethality (10,14,32). This anticonvulsant effect of ketamine may be mediated by the NMDA system. However, other phencyclidine-like drugs exert significant proconvulsant activity in the same tests (17,19). In a recent study (37), we found that ketamine in the dose 40 mg/kg loses the anticonvulsant effects of lower doses. This is in concordance with the results of the present experiment with topically applied PTZ. The receptor and/or molecular basis for this dualistic effect of ketamine is still unclear. One may speculate that nonspecific effects of ketamine on receptor systems other than NMDA may play a role. The difference in anticonvulsant action between ketamine and other PCP-like drugs may be explained by the presence of a narrow dose range for the anticonvulsant effect of other PCP-like drugs.

The fast activation of cortical focus and increased number of interictal cortical discharges by KET found in the present study corresponds with a previous article on amygdala-kindled seizures (limbic focus) in which ketamine dose dependently increased the frequency of interictal amygdala spiking in the early phases of kindling. Nevertheless, the same study described an anticonvulsant action of ketamine against fully developed amygdala-kindled seizures, that is, against ictal discharges (afterdischarges) with full motor seizures (4). Similar effects were obtained using phencyclidine in amygdala kindling (15). These, as well as our present results, may be explained by a hypothetical dualistic action of ketamine, which could have the following features: a) *dose dependency*—lower doses are anticonvulsant, higher doses proconvulsant (4); b) *dependence upon seizure model*—models of focal seizures are usually activated by ketamine [(3,12) also in the present topical PTZ experiment]. It appears that small neuronal populations (foci) in the amygdala or neocortex are coactivated by ketamine until a certain level of seizure generalization is reached. Large neuronal nets predominantly in the brainstem that are believed to be responsible for generalized tonic-clonic seizures (5,6,30) appear to be suppressed by ketamine (37); and/or c) *neuronal population dependence*—some neurons in the cortex (both neo- and paleo- may be excited by ketamine, which results in an increased epileptogenesis after topical application of the convulsant agent (28), whereas other neurons may suppress subcortical structures responsible for the genesis of generalized seizures. Of course, any combination of the aforementioned reasons is possible. Moreover, these results

demonstrate that there may be different mechanisms responsible for the generation of interictal and ictal events. These mechanisms may act against each other and are differently affected by ketamine. We published recently that ketamine can suppress electrically induced neocortical afterdischarges but does not influence paired-pulse potentiation and frequency potentiation discharges [i.e., individual events; (22)]. These data strongly suggest that mechanisms responsible for the generation of interictal events are different from those inducing long-lasting ictal discharges and afterdischarges.

The rhythmic activity induced by systemic pentylenetetrazol probably represents a special model of primary generalized seizures (21,23) that are resistant to ketamine pretreatment.

Topical application of pentylenetetrazol on the neocortex of freely moving rats represents a model of neocortical epileptic focus (i.e., simple partial seizure) that can be useful for the testing of the action of antiepileptic drugs on both interictal and ictal events. In the model of systemic pentylenetetrazol rhythmic activity, a further verification is necessary to demonstrate that this is the real model of human absences (39).

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