Pharmacology Biochemistry & Behavior, Vol. 14, pp. 27–33. Printed in the U.S.A.

Ketamine: Convulsant or Anti-Convulsant?[1]

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Received 27 March 1980

MYSLOBODSKY, M. S., V. GOLOVCHINSKY AND M. MINTZ. *Ketamine: Convulsant or anti-convulsant?* PHARMAC. BIOCHEM. BEHAV. 14(1) 27–33, 1981.—Ketamine hydrochloride in doses producing narcotic-cataleptic effects (50–100 mg/kg, IP) reduced the intensity of picrotoxin convulsions and eliminated seizures caused by metrazol administration. Subcataleptic doses (5–20 mg/kg) increased the duration of mitigated convulsive symptoms (abortive grand mal fits, jerks) especially those evoked by picrotoxin. Narcotic-cateleptic doses of ketamine considerably increased the duration of the period of single and multiple jerks produced by picrotoxin administration. Both convulsants transformed 1–2 Hz "ketamine complexes" into 2–4 Hz Wave-spike discharges which appeared in a quasi-periodic fashion alternating with periods of relatively suppressed electrocortical activity. Electroencephalographic grand mal patterns were typically dissociated from behavioral manifestations under 50–100 mg/kg of ketamine, followed by a short period of postictal depression and a rapid recovery of preseizure electrographic patterns. Findings suggest that mechanisms involved in seizure alleviation may be responsible for sustaining mitigated convulsive phenomena. Neuro-chemical processes underlying antiepileptic ketamine potency remain unknown.

Ketamine Metrazol Picrotoxin Status pathophysiology

KETAMINE is a rapidly-acting anesthetic and analgesic agent which is often used in the anesthesia of children [18]. This useful compound has fallen from favour due to observations of adverse psychic effects occurring during recovery in some individuals [8]. In addition, there are indications that ketamine may have epileptogenic properties [2, 7, 11], which further limit its scope as an anesthetic in pediatric patients. Although experimental evidence of epilepsy has been limited to "abnormal spiking and hypersynchronous bursting activity" produced in the course of one-three months daily administration, Manohar *et al.* [11] warn: "The ability to demonstrate these epileptiform patterns in mature, fully developed rats can be extrapolated to imply that even greater abnormal brain wave activity might be induced in the developing CNS. Since many of the procedures in which pediatric patients receive ketamine anesthesia are related to neurosurgical or neurological diagnoses of suspected brain disease, it should be kept in mind that prolonged or multiple administration of ketamine for diagnostic procedures may induce some degree of iatrogenic damage to the CNS (p. 826)."

Ketamine administered intravenously in doses 2–4 mg/kg reportedly activated local limbic electrographic convulsions in a sample of adult epileptic patients with depth electrodes in the limbic structures. In three out of six patients motor manifestations of epilepsy have also been noted [7].

However, some practitioners have administered ketamine to epileptic patients without aggravating their state [3,4]. Furthermore, ketamine has been demonstrated to cause a dose-related transient suppression of the neocortical and hippocampal focal electrographic seizures in cats produced by penicillin [3]. Celesia *et al.* [3] came to the conclusion that "ketamine had no convulsant properties, but a rather mild antiepileptic effect (p. 352)." In a study by DeVore *et al.* [5], ketamine depressed the projected spiking of the cobalt focus. The effect of ketamine on the primary focus can be inferred from the rotation behavior of rats which was directed *towards* the cobalt focus. Typically the focal activity was observed in a quiet rather than actively moving animal suggesting that ketamine-induced rotation hardly aggravated interictal activity. In addition, ketamine causes rotation in the same direction as amphetamine [14]. Electrophysiological analysis indicated that circling is directed *towards* the less active hemisphere [19]. These findings suggest that cobalt-induced activity should be slowed down under ketamine in order to cause ipsilateral rotation. Considering this evidence it is difficult to accept the conclusion

[1]This study was initiated at the Reed Neurological Research Center, UCLA School of Medicine. Drs. J. Engel, Jr. and R. Ackermann generously provided their research facilities and assistance. This work was partially supported by a grant from Mr. H. Pardee and A. and E. Spiegel Family Foundation. We thank Ms. R. Tomer for manuscript assistance. Presented at the 10th Annual Meeting of the Society for Neuroscience, November 1980, Cincinnati, OH.

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that "when given in doses which correspond to an anesthetic state in the rat, ketamine induces a state of excitation which is at seizure threshold, p. 116." Informal observations in this laboratory did not reveal any sign of convulsive properties of ketamine. One may hypothesize however, that such effects may be detected when ketamine is administered *in the presence* of an increased brain excitability. Since paroxysmal EEG "ketamine complexes" are generalized and bilaterally synchronous [3, 14, 17], and their pattern resembles low frequency wave-spikes, one would anticipate that wave-spike electrographic phenomena and possibly also behavioral convulsions produced by metrazol and picrotoxin should be facilitated by ketamine. This hypothesis suggested by previous studies [13] was tested experimentally in the present study. The advantage of exploring ketamine against these two convulsants is that despite certain similarity of their electrographic patterns, they probably act on different neurotransmitter mechanisms. Picrotoxin is known as the antagonist of the GABAergic system while metrazol does *not* seem to act on GABA receptors [10] at least beyond the spinal level.

METHOD

Subjects and Materials

Male Sprague-Dawley rats (450–550 g) (n=50) and male Wistar rats (200–300 g) (n=10) were housed one to a cage in a standard laboratory environment with food and water ad lib. Night-day cycle (12 hr darkness/12 hr light) was maintained by artifical lighting.

The following compounds were used: ketamine hydrochloride (Parke-Davis), picrotoxin (Abbott), metrazol (Knoll). The doses given in the text refer to their salts.

Procedure

Animals were assigned to two groups, one injected with metrazol and one with picrotoxin. The former group was composed exclusively of Sprague-Dawley rats while the latter also included Wistar rats.

Metrazol-ketamine interaction. Following an initial dose of 20 mg/kg of Metrazol administered intraperitoneally, the rat was placed in the rotometer bowl for observations of seizure behavior. Injections were repeated every 5 min with a dose of 10 mg/kg until the development of the generalized fit ("grand mal"). Six major convulsive symptoms were assessed and graded in points as follows: (1) rhythmic ear twitches (one point), (2) myoclonic head-body jerks (two points), (3) multiple head-body jerks (three points), (4) partial tonic seizure (four points), (5) maximal (grand mal) convulsion (five points), (6) multiple seizures ("status") (six points).

A pilot study conducted with ten rats demonstrated that minor myoclonic events, i.e. ear twitches and head-body jerks, occurred after 20–30 mg/kg of metrazol. Grand mal did not develop until the dose reached 40 mg/kg. With 50–60 mg/kg rats generated recurrent seizures.

A dose of 50 mg/kg of metrazol was used in the major portion of the study. In the latter, each rat was pretreated with 0.9% of saline or with 5, 10, 20, 50, or 100 mg/kg of ketamine (five rats per dose) given intraperitoneally in the same volume of 0.9% saline. Two-three min later, or at signs of the rats' excitation and rotation [14,17], a challenging dose of Metrazol (50 mg/kg) was injected and the six major convulsive symptoms were assessed.

Each rat received an appropriate score and the group score was computed and referred to a dose for the correlation analysis.

Ketamine-picrotoxin interaction. Due to a long latency of picrotoxin effects it was administered 8–10 min prior to 0.9% saline (control animals) or ketamine. Three doses of ketamine (in the same volume) were used: 20, 50 and 100 mg/kg. Picrotoxin was used in a dose of 4 mg/kg. Experiments were conducted in the same environment and convulsive symptoms were rated as described above, except that the rhythmic ear twitches stage was omitted, and instead the first "sedation phase" was assessed [16].

Surgery. Eight rats from the Sprague-Dawley sample were implanted with cortical electrodes. Three of them were used for the electroencephalographic analysis of ketamine effects and its interactions with metrazol and the remaining five were examined for picrotoxin-ketamine interaction effects.

Rats were anesthesized with ketamine (Ketalar) (100 mg/kg, IP) followed by xylazine (Haver-Lockhard) (20 mg/kg IM) and placed in a Kopf stereotaxic instrument. Four holes for recording electrodes located over symmetrical points of the visual cortex (4 mm laterally to midline and 7 mm caudally from bregma) and sensorimotor cortex (1 mm rostrally from bregma and 3 mm laterally to midline) were drilled with precautions taken to avoid dura damage. Two holes for anchoring stainless steel jeweller's screws were drilled on the midline over the frontal cortex and over the cerebellum. An additional hole for an indifferent electrode was drilled over the cerebellum on the midline. The cortical and indifferent electrodes were silver balls presoldered to Amphenol microminiature pins.

Rats were taken to the experiment five–seven days after surgery. EEG was recorded with a Grass Model 8 EEG machine (band-width 0.3–30 Hz).

RESULTS

KETAMINE EFFECTS

Behavior

All animals injected with ketamine in doses of 5–100 mg/kg developed a characteristic progression of decreasing hyperactivity and increasing stereotypy as a function of dose: rotation, head swinging, head nodding, immobility in ataxic posture. With doses 50–100 mg/kg stereotypic behavior and vigorous rotation occurred with a latency of 1–2 min and lasted for 2–3 min being interrupted by loss of righting reflex and cataleptic immobility signalling the beginning of narcotic phase, which lasted 20–40 min; 2–4 min after termination of the narcotic phase a new period of vigorous rotation developed, lasting 10–30 min. None of the animals displayed any signs of behavior which would qualify as epileptiform at any ketamine dose used.

EEG Pattern

In agreement with previous reports, ketamine EEG effects were dose related. In low doses (5–10 mg/kg) ketamine produced spindle-shaped bursts of activity in the beta band (about 30 Hz) in the visual cortex and somatosensory cortex, intermixed with infrequent theta waves. Occasionally with doses of 20 mg/kg, and reliably with doses 50–100 mg/kg, ketamine produced a pattern of beta-theta activity which corresponded with phases of stereotypic behavior. Severe

ataxia and immobility were correlated with a pattern represented by slow wave-sharp wave 0.5–2 Hz complexes ("ketamine complexes" of Celesia *et al.* [3]) alternating with bursts of beta and theta activity in a quasi-periodic fashion. Not a single case of electrographic seizure was observed in the dose range of ketamine employed.

KETAMINE INTERACTION WITH CONVULSANTS

Behavioral Effects

Metrazol. A single dose of metrazol (50 mg/kg) administered prior to or after saline produced a spectrum of convulsive phenomena culminating in violent generalized tonic-clonic convulsions. Some of these convulsions were repetitive and in 60% of the cases, lethal.

Pretreatment of animals with ketamine or superimposition of ketamine immediately after metrazol injection mitigated convulsive symptoms (Table 1). This observation was supported by the ANOVA results which indicate the significance of the effect of the dose on the seizure score, $F(5,47)=10.69$, $p<0.001$. The Duncan New Multiple Range Test for the differences among means showed that the main difference was between saline and ketamine at doses of 20 mg/kg and higher.

The overall seizure score was inversely related to the dose of ketamine. Even the minimal dose of the drug converted full-blown grand mal convulsions into abortive seizures. Correlation $r(28)=-0.63$, $p<0.01$ was obtained for the dose-related attenuation of seizure intensity.

Two animals with a ketamine dose of 50 mg/kg and most of the rats which received doses between 10 to 20 mg/kg, developed jerks which, although not culminating in a full blown grand mal fit, continued during the whole 45 min period of observation. This phenomenon was far more salient in a study with picrotoxin.

Picrotoxin. In a dose of 4 mg/kg, picrotoxin followed by saline produced the whole spectrum of convulsive phenomena ("somnolence" stage, single and then multiple jerks, partial or full blown grand mal fit) in both Wistar and Sprague-Dawley rats. Following tonic-clonic episode the animal typically remained inactive for a 10–30 min period.

Ketamine effects are summarized in Table 2. It demonstrates that in a dose of 50 mg/kg ketamine mitigated convulsive symptoms, due to the elimination of the full blown grand mal fits in 9 out of 10 animals tested with this dose. In all of them, however, single or multiple jerks remained throughout the entire period of observation. They continued with about the same intensity during cataleptic stage and subsequent rotation period. A dose of 100 mg/kg eliminated even partial (abortive) tonic fits although an increase in the vitality of jerks was noted with this dose as well. The ANOVA results indicate highly significant effect of the ketamine dose, $F(3,23)=13.05$, $p<0.001$. Subsequent intercomparison by Duncan New Multiple Range proved that the main difference was between the effects of saline and ketamine at doses of 50 and 100 mg/kg (Table 2). Table 2 also demonstrates that in a

TABLE 1

KETAMINE EFFECTS ON METRAZOL-ACTIVATED SEIZURE SYMPTOMS

Ketamine dose	Mean convulsive symptom score (± SD)	% seizure decrease
0 (0.9% NaCl)	4.7 ± 1.06	
5	3.9 ± 1.91	17
10	3.9 ± 1.91	17
20	2.3 ± 0.87*	51
50	1.1 ± 0.50*	77
100	1.0 ± 1.10	79

*$p<0.05$ as determined by Duncan New Multiple Range Test.

TABLE 2

KETAMINE EFFECTS ON PARAMETERS OF PICROTOXIN-INDUCED SEIZURES (POOLED DATA FOR SPRAGUE-DAWLEY AND WISTAR RATS)

Seizure parameters (picrotoxin dose 4 mg/kg)	Ketamine dose (mg/kg) 0 (0.9% NaCl) (N=10)	20 (N=5)	50 (N=4)	100 (N=3)
Mean convulsive symptom score (± SD)	5.1 ± 0.30	5.8 ± 0.40†	4.7 ± 1.00*	3.2 ± 0.50*
Mean latency (min ± SD) to the 1st tonic-clonic (t-c) fit	17.25 ± 1.58	21.60 ± 7.70	24.50 ± 5.40	—
Number of repeated fits	0.1 ± 0.3	1.6 ± 1.14	0.5 ± 0.75	—
Duration of postical jerk period (after the 1st fit in min)	—	≥40	≥40	≥40

*Different from saline at $p<0.05$.

†Different from ketamine 50 and 100 mg/kg (as determined by Duncan New Multiple Range Test) at $p<0.05$.

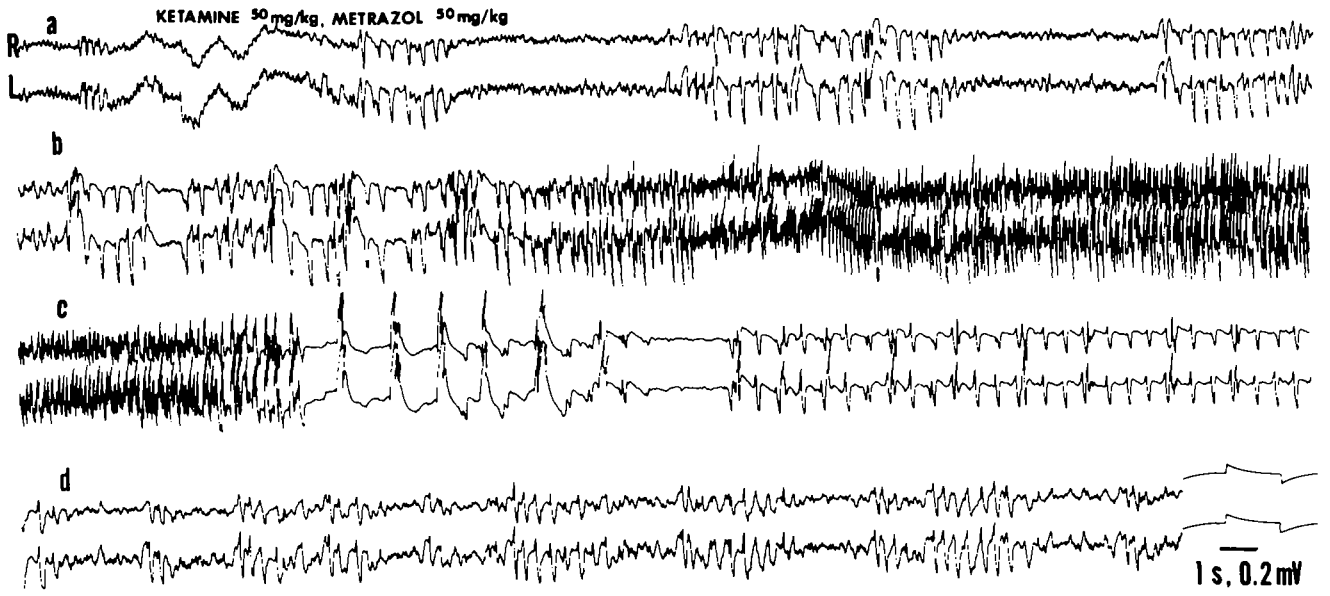

FIG. 1. Effect of metrazol (50 mg/kg, IP) administered during the first signs of rotation behavior produced by ketamine (50 mg/kg, IP). (a) Prolonged bursts of wave-spike discharges alternating with periods of relatively depressed electrical activity about 1 min after metrazol administration; (b) About 2 min later, disappearance of periods with depressed EEG between wave-spikes signalling an impending grand mal pattern; (c) Short-lasting period of postictal depression followed by the recovered ketamine preseizure pattern; (d) Observed 20 min after (c).

dose of 20 mg/kg ketamine did not alleviate the picrotoxin-induced convulsive symptomatology. On the contrary, three out of five animals tested with this dose, developed a steady pattern of multiple jerks which began about one min after ketamine administration and continued through the whole period of observation (40 min) interrupted by repetitive grand mal seizures. The development of multiple seizures or jerks proved to be a reliable phenomenon, $F(3,23)=6.54$; $p<0.005$.

ELECTROENCEPHALOGRAPHIC EFFECT

Metrazol

Metrazol administered after ketamine in a dose of 20 or 50 mg/kg caused an increase in the duration of bursts of "ketamine complexes" along with a parallel increase in their frequency. These complexes were actually transformed into frank seizure 2–3 Hz wave-spike discharges (Fig. 1), accompanied by occasional myoclonic phenomenon. The pattern of quasi-periodic alternation of these bursts with a more desynchronized activity following ketamine, accompanied not only cataleptic-narcotic phase but also pre- and postanesthetic circling.

As long as wave-spike bursts were interrupted by periods of desynchronised activity, no other seizure pattern developed. With an increase of the burst duration, periods of depressed EEG disappeared and wave-spikes gradually emerged as a dominant activity which eventually lead to the development of the electrographic grand mal pattern (Fig. 1). Grand mal patterns were not uncommon with both the 20 mg/kg and the 50 mg/kg doses of ketamine (Fig. 1). However, they were *not* accompanied by behavioral full blown seizures but were followed by a short period of postictal depression and an extremely rapid recovery of the preseizure EEG pattern (10–30 sec following ketamine vs several minutes after saline). None of the animals pretreated with 100 mg/kg developed electrographic grand mal seizure.

Picrotoxin

Ketamine in doses 20–100 mg/kg injected 8–10 min after Picrotoxin caused a transformation of irregular wave-spike discharges into quasi-periodic ketamine paroxisms alternating with periods of desynchronised activity. While ketamine imposed a periodicity, picrotoxin transformed "ketamine complexes" into typical 3–4 Hz wave-spike or multiple spike-wave discharges. As long as periods of desynchronisation were present, only myoclonic events were recorded during the period of rotation or cataleptic immobility. In all animals, however, irrespective of the dose of ketamine administered, wave-spikes eventually dominated, leading to the electrographic grand mal pattern (Fig. 2). The latter was accompanied by a mitigated form of behavioral grand mal convulsion, followed by a fast recovery of the initial EEG pattern and the resumption of myoclonus.

DISCUSSION

The results of the present study demonstrate that ketamine does not produce epileptiform phenomena of its own and moreover, alleviates the symptomatology of behavioral seizures caused by Metrazol and Picrotoxin, particularly when given in a dose which produces cataleptic phenomena. These findings are in agreement with the data of

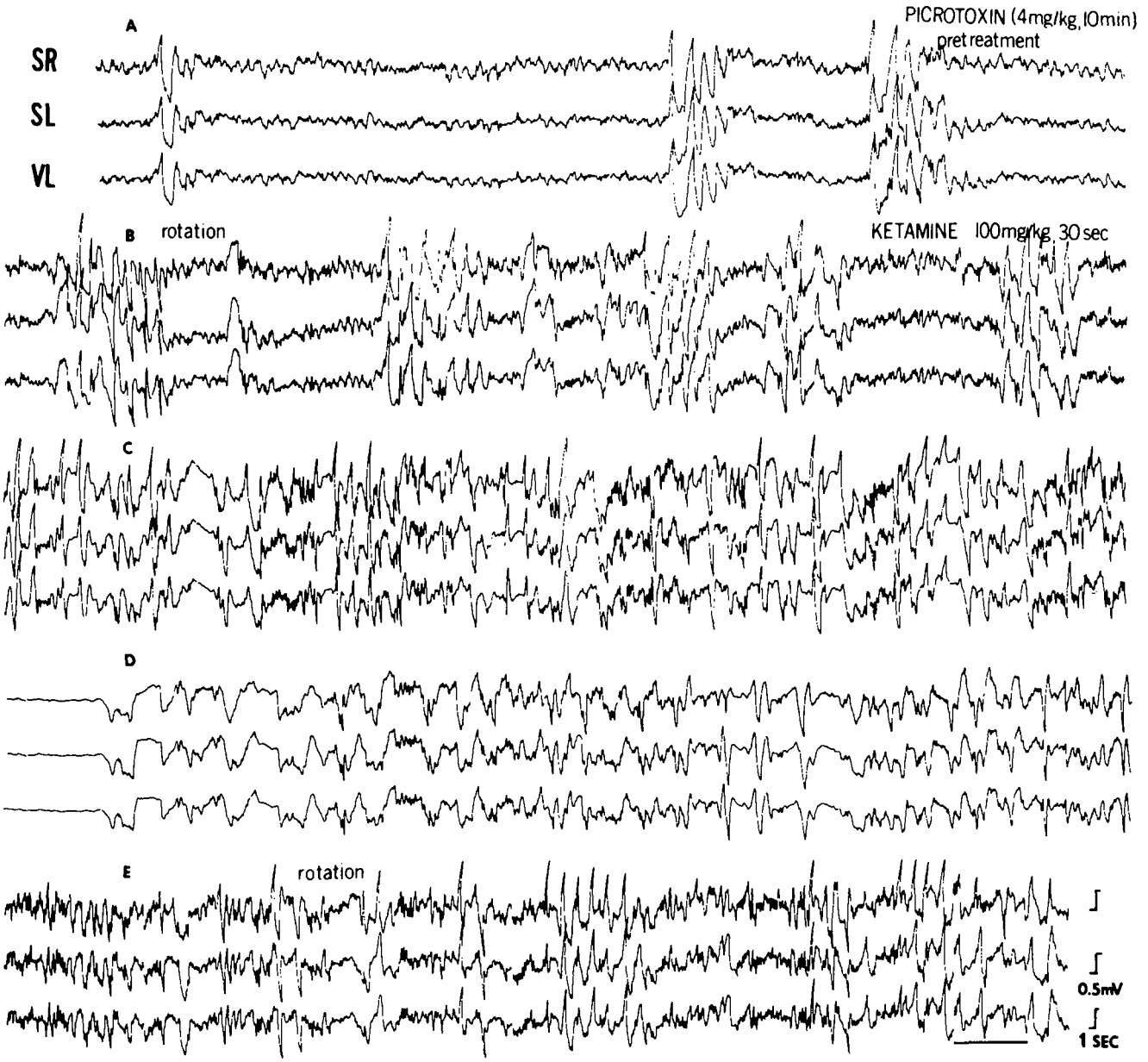

FIG. 2. Effect of ketamine (100 mg/kg, IP) administered about 10 min after picrotoxin (4 mg/kg, IP). (a) Irregular bursts of paroxismal discharges accompanied by somnolence; (b) Ketamine sets a quasi-periodic alternation of bursts of wave-spikes with relatively suppressed EEG about 30 sec after injection. The animals continue to circle vigorously; (c) The fragment of EEG taken about 37 min after (b) demonstrates a gradual disappearance of the depressed electrical activity between the wave-spike bursts which is followed by the development of the grand mal pattern (not shown). The latter was not accompanied by behavioral manifestations of grand mal; (d) Postictal depression with initial signs of the recovery of preseizure "burst-suppression" pattern; (e) A fragment taken 40 sec after (d)illustrates the full recovery of EEG and circling behavior. Single and multiple jerks interrupt occasional rotation of the rat during this stage.

Celesia *et al.* [3] and Taberner [21] suggesting that ketamine has certain antiepileptic potency.

The nature of the antiepileptic effects of ketamine is not clear. Ketamine is known *not* to act via the GABAergic system. To the contrary, it has been shown to decrease GABA synthesis by inhibiting the activity of glutamate decarboxylase [6]. In addition, ketamine increases 5-HT levels in various brain regions [22] which should act in the direction of promoting GABA catabolism by inhibiting the activity of GABA transaminase and decreasing GABA synthesis [1]. The inability of low doses of ketamine to protect against picrotoxin convulsions may be associated with its capacity to decrease the brain GABA tone. It is important to note, however, that although ketamine acts partially antagonistically to picrotoxin, it does not systematically aggravate picrotoxin convulsions. In other words, anticonvulsant properties of ketamine should be sufficiently pronounced to compensate for its GABA antagonistic properties.

A possible mechanism of ketamine anticonvulsant action could be gleaned from the fact that it produces vigorous and tight rotational behavior in non-lesioned rats [14,17]. Cirling has been attributed to the intrinsic asymmetry within the dopamine-containing nigrostriatal system [9] which is potentiated by compounds activating, either directly or indirectly, the dopaminergic activity.

Ketamine is believed to inhibit the high affinity transport system responsible for the uptake of norepinephrine [20]. Also it has been shown to increase striatal homovanillic acid which suggests an acceleration of dopamine turnover [22]. Both norepinephrine and dopamine systems have been implicated in epilepsy control (see [12] for review). Further experiments are required to clarify the contribution of catecholamine in antiepileptic effects of ketamine.

Unlike seizure intensity, the duration of mitigated convulsive phenomena appeared to be unusually prolonged under ketamine. This puzzling feature of ketamine effect deserves a special comment.

Quasi-periodic bursts of ketamine complexes were transformed into typical wave-spike discharges under the influence of metrazol. Our preliminary micro-electrode studies demonstrated that ketamine complexes as well as bursts of wave-spike discharges produced by convulsants have the same cellular organisation (Golovchinsky and Myslobodsky, unpublished). Most of the cells encountered during the development of both phenomena fired during sharp components and were inhibited during waves, suggesting that ketamine complexes as well as wave-spike discharges are caused by hypersynchronous IPSPs followed by rebound discharges in the depth of the cortex (see [13] for review). It is therefore to be expected that ketamine could potentiate electrographic phenomena evoked by both metrazol and picrotoxin while largely interfering with behavioral manifestations of convulsions. Given the electrographic picture of quasi-periodic wave-spike discharges accompanied by repetitive myoclonic events the whole picture qualifies for designation as experimental status. Repetitive seizures were also observed in animals pretreated with GABA-transaminase inhibitors when a challenging dose of metrazol was administered [15]. These GABA-transaminase inhibitors are potential anticonvulsants and their only similarity to ketamine is that they produce a stable electrocortical synchronisation. The bursts of quasi-periodic hypersynchronisation produced by ketamine probably act as a vehicle for temporary epileptiform activity, "chaining" it into its own unique stereotypic pattern. It is possible that this powerful hypersynchronisation recruits additional elements into seizure activity or facilitates the repolarisation of some active cells which otherwise would have ceased to convulse due to inactivation of impulse-generating mechanism [15]. This hypothesis may explain the short duration of postictal depression and fast recovery of electrographic and behavioral convulsive phenomena under ketamine.

On the basis of this evidence ketamine could hardly be designated as a convulsant unless the term is unjustly expanded. Although we would not recommend employing this drug in cases of epilepsy, it remains to be proven that in some cases where seizures were reported to have occurred under ketamine [7], they were provoked *due to* and not *in spite of* ketamine.

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