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Ketamine Suppresses Both Bicuculline- and Picrotoxin-Induced Generalized Tonic-Clonic Seizures During Ontogenesis

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VELÍŠKOVÁ, J., L. VELÍŠEK, P. MAREŠ AND R. ROKYTA. *Ketamine suppresses both bicuculline- and picrotoxin-induced generalized tonic-clonic seizures during ontogenesis.* PHARMACOL BIOCHEM BEHAV **37**(4) 667–674, 1990.—An anticonvulsant action of ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) antagonist (5–40 mg/kg IP), on the bicuculline-induced (3–8 mg/kg IP) or picrotoxin-induced seizures (3–6 mg/kg IP) was assessed in male Wistar rats aged 7, 12, 18, 25 and 90 days. Ketamine alone caused moderate ataxia which was more pronounced in younger animals. In combination with both aforementioned convulsants, ketamine exerted anticonvulsant effects against generalized tonic-clonic seizures in all developmental stages studied. This effect was more pronounced in bicuculline-treated animals. Moreover, ketamine also suppressed the lethality induced by both drugs during all the development. On the contrary, the action of ketamine on minimal (clonic) seizures was moderate or absent. Our results suggest an important role of ketamine-affected transmission in the generation of the generalized tonic-clonic seizure pattern; moreover, an action of high doses of ketamine on GABA-A receptors might be present.

Ketamine Picrotoxin Bicuculline Ontogenesis Rat Seizure

KETAMINE (KET), a drug used in human anesthesiology, is an antagonist at N-methyl-D-aspartate (NMDA) receptor (1, 16, 28) for excitatory amino acids (8). Moreover, an antagonism at muscarinic receptors has been found (15). Ketamine also acts at sigma opioid receptors, but the potency is about 40 times less than potency for binding at the PCP site which forms a part of the NMDA receptor complex (32). The KET-induced inhibition of neuronal uptake of serotonin and noradrenaline has been also noted (24).

The anticonvulsant action of KET has been studied extensively. A number of studies found KET to be anticonvulsant in various seizure models, e.g., in maximal electroshock seizure model (22), in models induced by systemic application of chemical convulsants: picrotoxin, pentylenetetrazol, and 3-mercaptopropionic acid (11, 21, 27). All these aforementioned studies were conducted on adult animals. However, a rather different situation can be found in pups (18). For instance, almost all chemical convulsants produce two different types of epileptic seizures: 1) minimal seizures characterized by clonic convulsions of muscles of the head and forelimbs, whereas the righting ability is preserved; some authors consider this type of seizure to be the model of human absences (25); 2) major seizures (generalized tonic-clonic) usually beginning with running followed by a loss of posture then the tonic phase starts and after some seconds the long-lasting clonus of all limbs occurs.

The latter type of seizure is observed during the whole ontogenesis (18), whereas the former type is regularly seen beyond a certain stage of the animals' maturation. This stage is different for different convulsants. For example, both picrotoxin and bicuculline (acting as antagonists of GABAergic inhibition) produce minimal as well as major epileptic seizures. Bicuculline evokes minimal seizures at ages beyond the end of the second postnatal week of the rat, whereas picrotoxin is able to induce this type of seizure even at the end of the first postnatal week (26,33).

In our recent study (31), we have found KET to be extremely active in the suppression of generalized tonic-clonic seizures induced by pentylenetetrazol during the whole ontogenesis (starting with postnatal day 7). On the other hand, KET did not affect minimal, clonic seizures induced by pentylenetetrazol. In order to reveal if this was the specific anti-pentylenetetrazol action or the general action against the generalized tonic-clonic seizure type, we decided to perform this study dealing with the ontogenetic effects of KET against picrotoxin- and bicuculline-induced seizures.

METHOD

The experiments were conducted on 369 male Wistar albino

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rats. The animals formed five age groups: 7, 12, 18, 25, and 90 (adult) days old. Day of birth was taken as zero.

Control groups of animals received either bicuculline (BIC, Sigma) or picrotoxin (PX, Sigma) in the doses shown in Table 1. The dosage was based on the previous experiments of our group (26,33). Bicuculline was dissolved in 0.1 M HCl, pH was adjusted by 0.1 M NaOH to 5.5. Picrotoxin was dissolved in physiological saline. Both drugs were applied intraperitoneally in a volume of 2 ml/kg of body weight.

The experimental groups were pretreated with ketamine (Narkamon R, Spofa; KET) in the doses of 5, 10, 20, or 40 mg/kg IP. The highest dose of KET (40 mg/kg) was used only in 25- and 90-day-old rats. Ketamine was applied in the volume of 1 ml/kg 30 min prior to the application of both aforementioned convulsants. Following the application of the convulsant, the animals were placed into the separated cages and they were observed in the case of BIC for 30 min, and in the case of PX for 60 min. The cages for pups (7, 12 and 18 days old) were heated by an electric pad to maintain the body temperature. Observations were made by two experienced observers (J.V., L.V.) simultaneously.

We registered the incidence and measured the latency of the following phenomena (19): 1) Minimal (clonic) seizures without the loss of righting ability. In very young pups this type of seizure was often evaluated as imperfect, i.e., restricted on the half of the body. 2) Generalized tonic-clonic (major) seizures. They began as a rule with short running. Then the animal lost its righting ability and a short tonic phase occurred. Following the period of tonus the long clonic phase of all four limbs was observed.

Moreover, according to the following scale, we assigned a score (representing maximal behavioral pattern accomplished or severity of seizure) to each animal (23): 0—no changes in behavior; 0.5—abnormal behavior (sniffing, intensive washing, orientation); 1—isolated myoclonic jerks; 2—atypical (unilateral or incomplete) minimal (clonic) seizure; 3—fully developed minimal seizure; 4—generalized tonic-clonic seizure pattern with suppressed tonic phase; 5—fully developed tonic-clonic seizure.

The values were evaluated by means of ANOVA and further comparison was made by Tukey studentized range method [latencies; (20)] or by Fisher's exact test [incidence; (12)]. Scores were evaluated by nonparametric Kruskal-Wallis test (14). The level of significance was set to 5%.

RESULTS

Control Rats Treated With Bicuculline (BIC)

Minimal seizures were regularly elicited since the 3rd postnatal week of the rat. The incidence of these clonic seizures was extremely low in 7- and 12-day-old pups. Also, adult rats exerted these seizures sparsely (Table 1). On the contrary, major seizures were elicited by BIC since the early postnatal period in a sufficient amount, their incidence varied from 80 to 100% during the whole ontogenesis (see Table 2). The motor pattern of both seizure types did not differ from that described in the Method section. The seizure severity represented by a score varied between 4 and 5 points in all age groups. The lethality range was between 50–100% with the exception of the 18-day-old rats where the lethality was extremely low (Table 3).

Control Rats Treated With Picrotoxin (PX)

The small percentage of minimal seizures was observed within the first two postnatal weeks, their number was higher in 7-day-old rats than in 12-day-old ones. The incidence of generalized tonic-clonic (major seizures) was high at all the developmental stages studied. The score reflected the high incidence of major seizures with pronounced tonic phase and reached nearly 5 points in all the groups. The lethality of the animals varied between 50 and 100%. The motor phenomena observed following the PX treatment did not differ from those observed in our previous studies (26) and described above.

TABLE 1

THE EFFECTS OF KETAMINE ON THE INCIDENCE OF MINIMAL SEIZURES INDUCED BY BICUCULLINE (TOP) AND PICROTOXIN (BOTTOM)

Age	7	12	18	25	90	Days
BIC	4	4	4	8	8	mg/kg
Controls	0/10	1/11	8/10	6/9	4/11	
KET 5	0/8	6/8*	3/8	8/8	4/8	
KET 10	2/8	2/8	9/9	7/9	7/9	
KET 20	0/8	2/8	8/10	5/9	7/8	
KET 40	x	x	x	x	6/12	
Age	7	12	18	25	90	Days
PX	4	4	3	5	6	mg/kg
Controls	2/8	0/8	7/8	8/8	8/8	
KET 5	0/8	6/8*	7/8	8/8	8/8	
KET 10	3/8	4/11	6/8	8/8	8/8	
KET 20	1/8	6/8*	7/8	7/8	8/8	
KET 40	x	x	x	4/8*	7/8	

Columns represent age groups, rows show the doses of ketamine used. x: not tested. An asterisk denotes the significant difference in comparison with the control group ($p<0.05$).

The first number denotes the amount of animals with pronounced phenomenon in question; the second number indicates a number of animals in the subgroup.

Groups Treated With the Combination of KET and BIC

The KET pretreatment led to the dose-dependent ataxia in all

TABLE 2

THE EFFECTS OF KETAMINE ON THE INCIDENCE OF MAJOR (GENERALIZED TONIC-CLONIC) SEIZURES INDUCED BY BICUCULLINE (TOP) AND PICROTOXIN (BOTTOM)

Age	7	12	18	25	90	Days
BIC	4	4	4	8	8	mg/kg
Controls	8/10	10/11	10/10	9/9	9/11	
KET 5	8/8	5/8	1/8*	8/8	5/8	
KET 10	8/8	8/8	7/9	6/9	4/9	
KET 20	3/8	4/8	6/10*	4/9*	1/8*	
KET 40	x	x	x	x	3/12*	
Age	7	12	18	25	90	days
PX	4	4	3	5	6	mg/kg
Controls	7/8	8/8	8/8	8/8	8/8	
KET 5	7/8	7/8	7/8	8/8	6/8	
KET 10	7/8	11/11	8/8	7/8	8/8	
KET 20	6/8	8/8	8/8	2/8*	8/8	
KET 40	x	x	x	8/8	2/8*	

For details see Table 1.

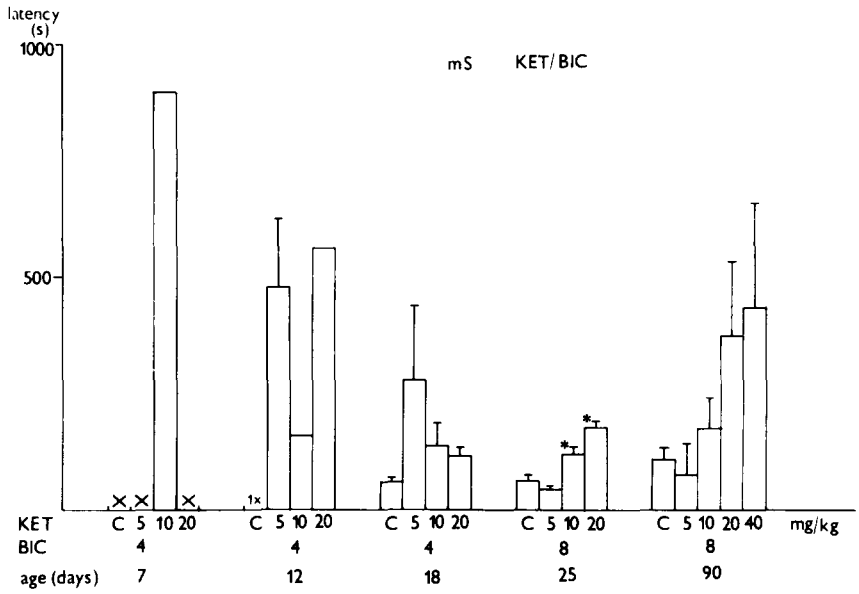

FIG. 1. The action of ketamine on the latencies of bicuculline-induced minimal seizures (mS). Mean+S.E.M. Abscissa: groups of columns represent age groups 7, 12, 18, 25 and 90 days; numbers in the row denoted 'BIC' show the dose of bicuculline used in each age group; row 'KET' denotes the doses of ketamine used; C: denotes control animals (convulsant only). Ordinate: latency of the phenomenon in seconds. Where the bars representing S.E.M. are absent we had an insufficient amount of data for statistics; x: denotes that the sign was not observed; 1x: the sign was registered only once. An asterisk indicates the significant difference ($p<0.05$) in comparison with the appropriate control group.

animals. Moreover, an increased incidence of minimal seizures was observed in all age groups. However, all these results were trends; statistical significance was reached only in 12-day-old pups with 5 mg/kg of KET. The latencies of minimal seizures if observed in a sufficient number for the statistical analysis were lengthened only in 25-day-old rats following the doses of 10 and 20 mg/kg of KET (Fig. 1).

Ketamine exerted substantially different effects against major seizures. The pretreatment with KET markedly decreased the incidence of major seizures in a dose-dependent manner in 25- and 90-day-old rats (with the exception of 40 mg/kg dose of KET). In 7-, 12-, and 18-day-old animals the depression of the incidence was not so marked and dose dependent as in both two older age groups; nevertheless, the highest dose of KET used decreased the incidence of major seizures significantly in 18-day-old rats. The prolongation of the latencies of the major seizures was observed in the animals up to 25 days of age following the doses of 10 mg/kg of KET and higher. However, two exceptions were noted: In 12-day-old pups the doses of 5 and 20 mg/kg of KET increased the latencies of major seizures (a dose of 10 mg/kg did not significantly lengthen the latencies probably due to a large variance of data). In 18-day-old rats, only the dose of 20 mg/kg of KET significantly increased the latency of the major seizures (Fig. 2).

The significant decrease of score was detected in all age groups after the highest doses of KET used (i.e., 20 or 40 mg/kg). In addition, in 18-day-old animals, all doses of KET decreased the score, in 25-day-old rats the dose of 10 mg/kg of KET was active (Fig. 3).

The lethality of the animals treated with bicuculline was extremely decreased following the KET pretreatment. The dose of 20 mg/kg of KET prevented the lethality with the exception of one animal 25 days old and one adult animal.

Groups Treated With a Combination of KET and PX

The situation very similar to that seen in BIC-induced seizures was observed in PX-treated animals. An increased incidence of minimal seizures was registered after the KET pretreatment in 7, and especially in 12-day-old rat pups. In the other age groups, the incidence of minimal seizures was not affected substantially. The significant increase of the latencies of minimal seizures was noted in 18-day-old pups following the doses of 10 and 20 mg/kg of KET (Fig. 4).

The incidence of major seizures was suppressed only in 25-day-old animals (20 mg/kg of KET) and in the adults (40 mg/kg dose of KET). The latencies of major seizures were significantly enhanced in 12-day-old pups (all doses of KET) and in 18-day-old pups (effective only the doses of 10 and 20 mg/kg of KET; Fig. 5).

The prominent action of ketamine on the seizure severity was seen in 25- and 90-day-old rats, where all doses of KET decreased the mean score with the exception of 10 mg/kg of KET in the 90 days old rats (Fig. 6).

Ketamine in all age groups decreased the lethality. The effects were seen predominantly in the animals aged 18 days and younger; however, the prolongation of the survival time was detected in 25- as well as in 90-day-old rats, significant in comparison with the controls (Fig. 7).

DISCUSSION

In our experiments KET was able to suppress major seizures

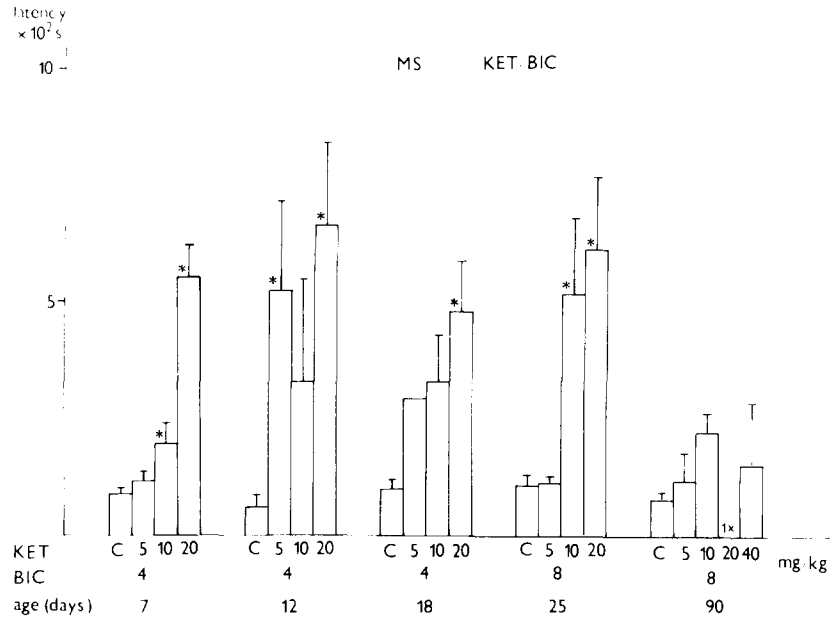

FIG. 2. The effects of ketamine on the latency of major (generalized tonic-clonic) seizures (MS) induced by bicuculline. Mean+S.E.M. For details see Fig. 1.

elicited by BIC or PX beyond the first or second postnatal week, respectively. Minimal (clonic) seizures were affected only moderately. Their increased incidence was noted in 12-day-old rats. Lethality was decreased following KET pretreatment since 12 days of age in BIC-treated animals and since 18 days of age in PX-treated animals.

The attenuation of major seizures and a little action of KET on minimal seizures agree with previous studies (3, 11, 21, 31). In our recent study (31), we have found KET to prevent tonic-clonic pentylenetetrazol-induced seizures during ontogenesis, i.e., the same seizure pattern which was suppressed after the application of both BIC and PX. The present study supports the recent data that KET suppresses tonic-clonic seizure pattern in general (21,31). Two reasons might play a role: 1) transmitter systems affected by KET play a role in the generation or modulation of major tonic-clonic seizures; 2) KET acts predominantly in specific structures which are responsible for the genesis of major tonic-clonic seizures and the structures generating minimal seizures are not af-

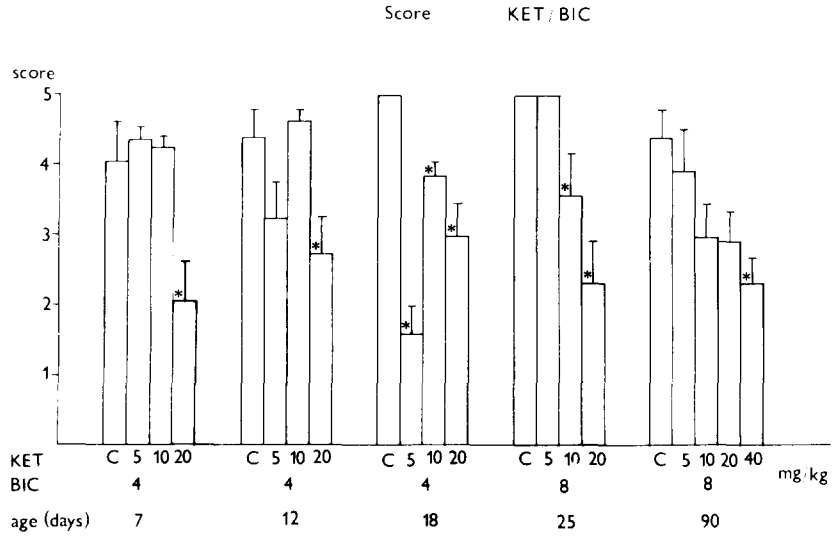

FIG. 3. The score (maximal behavioral pattern accomplished) of bicuculline-induced seizures and the influence of ketamine. Mean+S.E.M. Abscissa: see Fig. 1. Ordinate: score in points. Where the bars representing S.E.M. are absent all the values in the group were same. Asterisk denotes significant differences ($p<0.05$) in comparison with the control group.

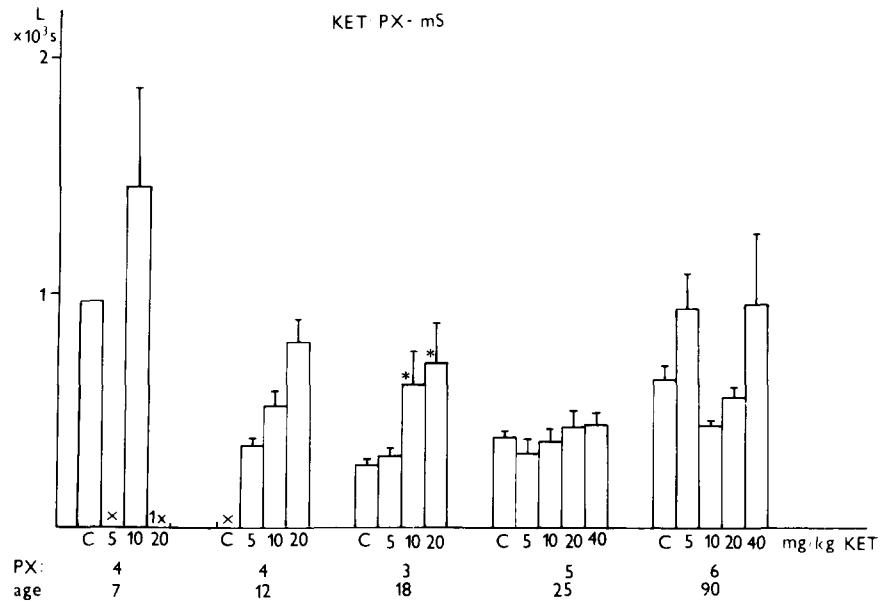

FIG. 4. The effects of ketamine on the latencies of picrotoxin-induced minimal seizures (mS). Mean+S.E.M. PX: denotes the doses of picrotoxin (in mg/kg) used in each age group. Other details see Fig. 1.

fected by KET. The attempts to localize the structures have been done (5, 6, 9). Nevertheless, a combination of both aforementioned reasons is also possible.

In the seventies the action of KET on serotonergic, dopaminergic and noradrenergic transmission was reported (10,30). Recently, novel data demonstrated the effects of KET at the level of NMDA receptor complex (1, 16, 28). Findings of the present study concerning the strong suppression of BIC- and PX-induced lethality as well as the prolongation of survival time after PX might suggest also another site of ketamine action, i.e., GABA(A) receptor complex. The ontogenetic development of the GABA(A) receptor complex components (7,17) might account for the differences between BIC- and PX-treated animals found in present study. However, benzodiazepines and barbiturates [the drugs affecting GABA(A) receptor complex] are able to suppress both minimal and major seizures during the whole development (Kubová et al., unpublished). In conclusion, the GABA effects of KET require further verification.

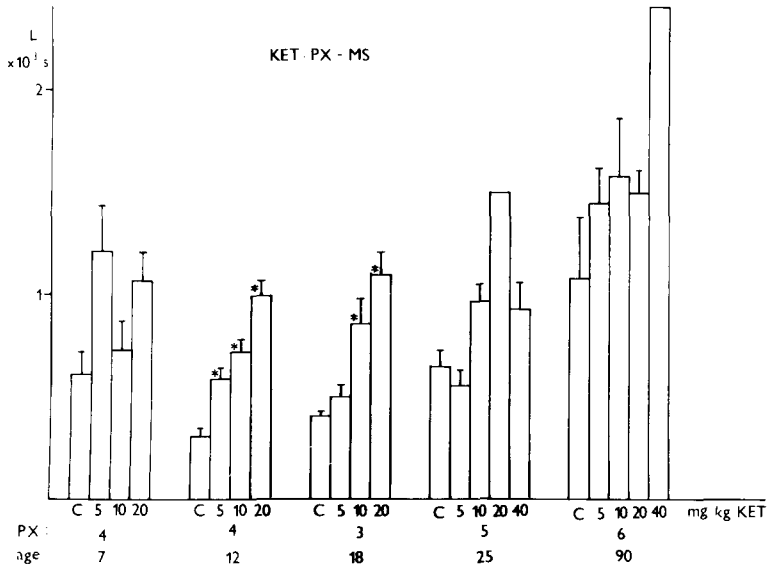

FIG. 5. The action of ketamine on the latencies of generalized tonic-clonic (major) seizures induced by picrotoxin. Mean+S.E.M. For details see Fig. 4.

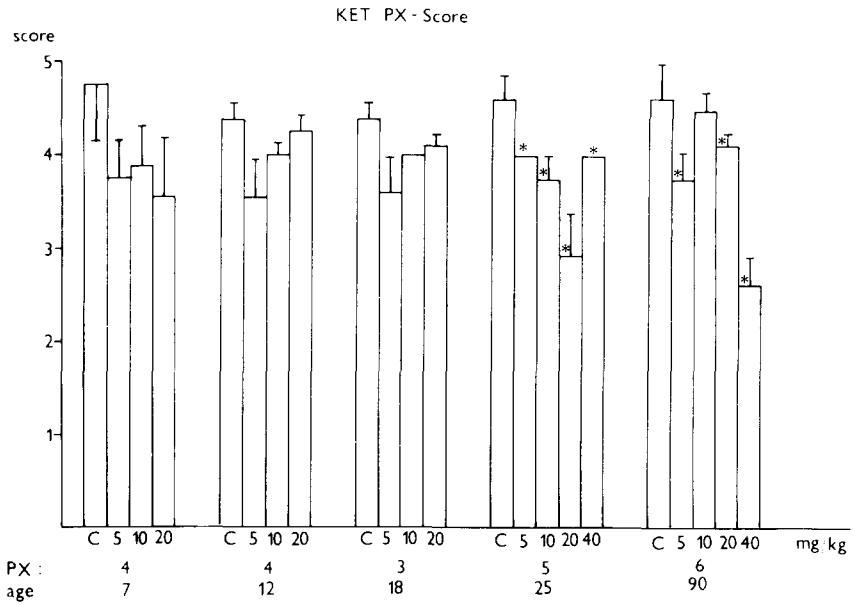

FIG. 6. The action of ketamine on seizure severity (score) of picrotoxin-induced seizures. Mean+S.E.M. PX: indicates the dose of picrotoxin used in each age group. For other details see Fig. 3.

At the age of 12 days we found an increase in the incidence of minimal seizures after KET pretreatment (combinations KET5/BIC, KET5/PX and KET20/PX). This finding might be explained on the basis of overlapped minimal seizures in controls by the rapid appearance of generalized tonic-clonic seizures. The blockade of tonic-clonic seizures by KET might unmask minimal seizures which appeared more frequently. Another explanation might result from the different ontogenesis of the structures responsible for both types of seizures (i.e., minimal and major).

The anticonvulsant activity of KET against major (tonic-clonic) seizures induced by both convulsants was demonstrated. This activity is probably dose dependent in BIC- as well as in PX-treated animals. An exception was found in 12-day-old rats treated with BIC where large variance of data (KET 10/BIC) probably sup-

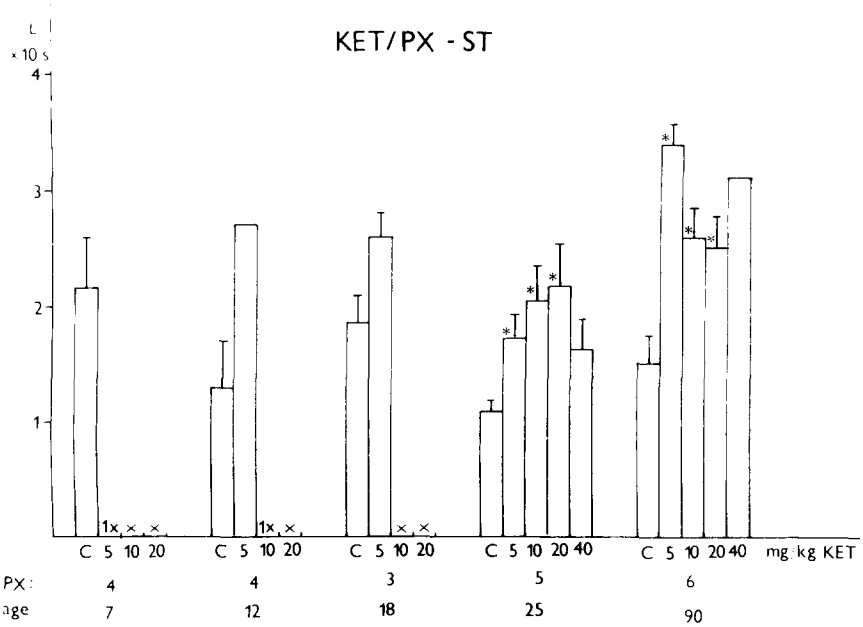

FIG. 7. The ketamine-induced effects on survival time (ST) following the application of picrotoxin. Mean+S.E.M. For details see Fig. 4.

TABLE 3

THE INFLUENCE OF KETAMINE ON THE LETHALITY FOLLOWING BICUCULLINE (TOP) OR PICROTOXIN (BOTTOM) APPLICATION

Age	7	12	18	25	90	Days
BIC	4	4	4	8	8	mg/kg
Controls	5/10	10/11	2/10	8/9	8/11	
KET 5	1/8	2/8*	0/10	0/9*	2/8	
KET 10	0/8*	2/8*	1/10	0/9*	3/9	
KET 20	0/8*	0/8*	0/10	1/9*	1/8*	
KET 40	x	x	x	x	2/12*	
Age	7	12	18	25	90	Days
PX	4	4	3	5	6	mg/kg
Controls	4/8	4/8	8/8	8/8	7/8	
KET 5	1/8	2/8	4/8*	8/8	6/8	
KET 10	0/8*	1/11	0/8*	5/8	6/8	
KET 20	0/8*	0/8*	0/8*	3/8*	6/8	
KET 40	x	x	x	4/8*	2/8*	

For details see Table 1.

pressed the statistical significance. Nevertheless, in 12-day-old pups treated with both PX and BIC, the dose of 5 mg/kg of KET significantly delayed major seizures (a difference in comparison with the other age groups). The difference might result from supersensitivity of NMDA receptors in young animals (29). Another exception was found in 7-day-old animals treated with PX, where 5 mg/kg of KET only insignificantly delayed major seizures and 10 mg/kg was completely ineffective. This might be explained on the basis of the loss anticonvulsant activity of relatively large dose of KET; however, without generally depressant effect. Similar situation was observed in adult animals following 40 mg/kg of KET in our recent study (31). The difference between the KET effects in PX- and BIC-treated 7-day-old pups might be caused by different mechanisms of seizure generation by convulsants.

In this model we have not observed any direct proconvulsant action of KET as reported previously (2,13). Only an attenuation of anticonvulsant effects was observed after the high doses of KET in 7- and 25-day-old rats following PX (10 and 40 mg/kg, respectively) and in 90-day-old rats following BIC (40 mg/kg of KET). Our results are in agreement with those finding ketamine to be anticonvulsant (3, 4, 11, 21, 27, 31).

The study presents the other data supporting an anticonvulsant profile of ketamine during ontogenetic development. The role of ketamine-affected transmitter systems in the genesis of generalized tonic-clonic seizures appears to be prominent; NMDA system might play a substantial role. Moreover, higher doses of ketamine (20–40 mg/kg) might influence GABAergic transmission as well.

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