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Effects of TCP on Spatial Memory: Comparison With MK-801

PIERRE FILLIAT[1] AND GUY BLANCHET

Centre de Recherches du Service de Santé des Armées, Unité de Neurotoxicologie, BP 87, 38702 La Tronche Cedex, France

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FILLIAT, P. AND G. BLANCHET. *Effects of TCP on spatial memory: Comparison with MK-801.* PHARMACOL BIOCHEM BEHAV **51**(2/3) 429–434, 1995. – TCP {*N*-[1-(2-thienyl)cyclohexyl]piperidine}, a PCP (phencyclidine) derivative, has been shown to possess antiepileptic and neuroprotective efficacy against chemically induced seizures. However, it is known that other antagonists of the NMDA receptor impair spatial learning. This study was thus undertaken to explore the eventual effects of TCP on memory. The same study was done with MK-801 {(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a,d*]-cyclohepten-5,10-imine}, one of the most studied NMDA receptor antagonists, which can be considered as a reference molecule. Three doses of each drug were chosen: 0.05, 0.1, and 0.2 mg/kg for MK-801 and 0.5, 1, and 2 mg/kg for TCP, the second dosage corresponding to the minimal required for antiseizure activity. The drugs were injected IP 30 min each day before a classical procedure of acquisition in a Morris water maze test. At the highest dose of each drug, the animals did not learn the position of the platform. At 0.1 mg/kg MK-801, the rats used a praxis strategy to find the platform but they did not know where the platform was. Contrary to MK-801, TCP at 1 mg/kg did not induce any memory impairment. At the lowest doses used, no memory impairment was found. It thus appears that, at the minimal therapeutic dose effective against chemically induced seizures (0.1 mg/kg for MK-801 and 1 mg/kg for TCP), TCP, contrary to MK-801, does not induce any memory impairment. Furthermore, at all the doses used, TCP presents the particularity that its locomotor side effects are not long lasting, being no longer observed from 30 min after the injection.

TCP MK-801 Morris water maze Spatial memory Motor behavior Open field Rats

IN RECENT YEARS, considerable attention has beeen focused on the role in physiological and pathologic mechanisms of the *N*-methyl-D-aspartate (NMDA) subclass of glutamate receptors. NMDA receptors are involved in developmental plasticity [see review in (27)]. Furthermore, the NMDA receptor has been proposed to be critically involved in mediating long-term potentiation (LTP), a long-lasting increase in synaptic efficacy induced by brief, high-frequency afferent stimulation (4). This LTP may reflect an important mechanism of information storage in the forebrain (5,23,26). On the other hand, NMDA receptors play a special role in epileptic activity [see (36) for review] and there is accumulating evidence that selective neuronal death after ischemia (37,38), hypoglycemia (2,45), and epilepsy (16,31) is mediated by the NMDA receptor. Therefore, various NMDA antagonists have shown positive effects as anticonvulsant, anti-ischemic, and neural protective drugs (6,10,13,24,30,33).

In this view, (+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a,d*]-cyclohepten-5,10-imine (MK-801), a noncompetitive NMDA receptor antagonist widely used as a neuroprotective [e.g., (31)] and antiepileptic drug [e.g., (15,25,32)], was shown to block LTP induction after systemic administration (1,12,34). Additionally, Morris et al. (29) demonstrated that intraventricular administration of the NMDA receptor competitive antagonist DL-2-amino-5-phosphonopentanoic acid (AP5) caused a behaviorally selective impairment of spatial learning in rats correlated with a blockade of LTP in the hippocampus. In vivo administration of antagonists of NMDA receptor may thus impair LTP and subsequent spatial learning. On the other hand, effects such as ataxia and stereotypies (increased locomotion, head weaving, and circling in the rat) in animals (18,40,41) or psychomimetic effects in humans (8) have been observed after administration of noncompetitive NMDA antagonists. Altogether, it thus appears that despite the effectiveness of noncompetitive NMDA antagonists in test systems that evaluate anticonvulsant and neuroprotective activity, such compounds often have neurobehavioral toxicity.

Recently, *N*-[1-(2-thienyl)cyclohexyl]piperidine (TCP), a

[1] To whom requests for reprints should be addressed.

compound that is structurally related to phencyclidine (PCP), one of the most specific ligands of the ionic channel associated to the NMDA receptor (42), has been found to possess various therapeutic properties (11,20–22), including anticonvulsive and neuroprotective effects against chemically induced seizures [e.g., (3,9,19)].

The present investigation was thus undertaken to assess the possible behavioral effects of TCP on learning. MK-801 is one of the most studied NMDA receptor antagonist. So the same study was done with MK-801, which can be considered as a reference molecule. The Morris water maze task was chosen for its particular sensitivity to perturbations concerning the NMDA receptor [see (7) for review]. Spontaneous locomotor activity was also tested to verify the specificity of the drug effects on learning and to eliminate possible bias in the interpretation of the performance in the Morris water maze task.

METHOD

Animals

Fifty-six male Wistar rats weighing 200–220 g at the beginning of the experiment were used as subjects. Rats were maintained in hanging cages (three to five per cage) with food and water freely available in a light-controlled animal room (lights on from 0700 to 1900 h). All tests were conducted during the light portion of the cycle.

Apparatus

The Morris water maze consisted of a circular pool (diameter: 140 cm, depth: 45 cm). The pool was filled to a depth of 25 cm with water at 21 ± 2°C, which was rendered opaque by the addition of milk. The hidden platform was a circular Plexiglas stand (diameter: 11 cm) submerged 2 cm below the water surface so that it was invisible at water level.

The open field consisted in a 90 × 90 × 40 cm flat black PVC box.

The rats' behavior was recorded and analysed by two CCD cameras (one for the water maze and the other for the open field) connected to a computer-assisted image processor (video-track, View-Point, Lyon, France).

Drugs

MK-801 (Merck Sharp and Dohme, Natick, MA) and TCP (a generous gift of Dr Kamenka, Ecole Nationale de Chimie, Montpellier, France) were used. Both were dissolved in 0.9% saline. Three doses of each drug were chosen: 0.05, 0.1, and 0.2 mg/kg for MK-801 and 0.5, 1, and 2 mg/kg for TCP. In each series, the second dosage corresponds to the previously demonstrated minimal dose required for antiepileptic and neuroprotective efficacy against chemically induced seizures (19,39). Drugs were administred IP daily, 30 min before each trial.

Procedure

Phase 1: habituation. During 1 week the animals were habituated by being handled twice a day.

Phase 2: the open field. Thirty minutes after the injection, each animal was placed in the open field and the recording system analysed the distance covered during 30 min in 5-min phases. During the first minute of each 5-min phase, the degree of ataxia was noted according to a scale (14) derived from Sturgeon et al. (40): 0—inactive or coordinated movements; 1—awkward or jerky movements or loss of balance while rearing; 2—frequent falling or partial impairment of antigravity reflexes; 3—inability to move beyond a small area, and support of body weight on haunches or abdomen; 4—inability to move except for twitching movements.

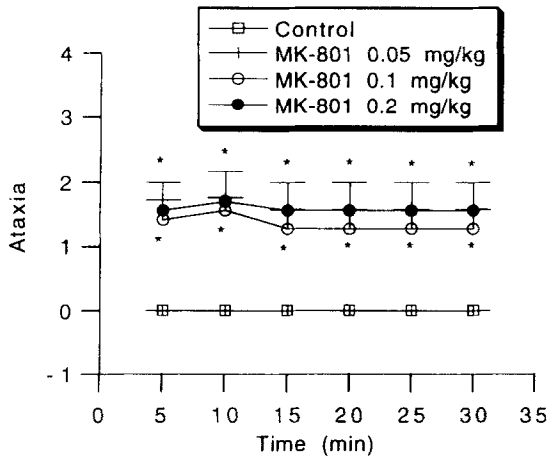

FIG. 1. Evolution of the ataxia degree for control and MK-801-treated rats. (The degree of ataxia was noted according to a scale derived from Sturgeon et al., see Procedure section). *Significantly different from the 0.05-mg/kg and the control groups ($p < 0.05$, Mann-Whitney U-test).

Phase 3: washout phase. Memory impairment has been reported to disappear 4 days after the injections of NMDA antagonists (17). For more security, the water maze test was performed 10 days later because the same rats were used for the two tests.

Phase 4: The Morris water maze test. Rats were allowed to swim freely until they found the escape platform. If a rat failed to find the escape platform within 60 s, it was placed on it by the experimenter. Between trials, rats were kept in individual cages under an IR lamp to minimize possible hypothermia. The intertrial interval depended on the time taken to test the other six rats. Each rat did a trial from each of the four starting points each day until an acquisition criterion was reached by its group (stable escape latency over 2 consecutive days). For each trial the rat was placed in the pool at one of four randomly determined starting locations; those locations were identical for all rats of all groups. During this period of test acquisition, the platform was located in a fixed position midway between the center and the edge of the pool (in the middle of quadrant 1). The time to reach the platform (latency) was recorded. This parameter was averaged for each block of trials and for each rat, whose daily performance was thus characterized. When the acquisition criterion was reached, animals performed a spatial probe trial. This trial consisted of removing the platform from the pool and allowing the rat to swim for 60 s in search of it. The time spent in each of the four quadrants of the pool was calculated as a percentage over 60 s. If the animal showed a persistent preference during this trial to swim in the pool quadrant where the platform had previously been placed, this was taken to indicate that the rat had acquired the spatial task and remembered it.

Statistical Analysis

The effects of drugs on locomotion in the open field were calculated by an analysis of variance (ANOVA) followed by

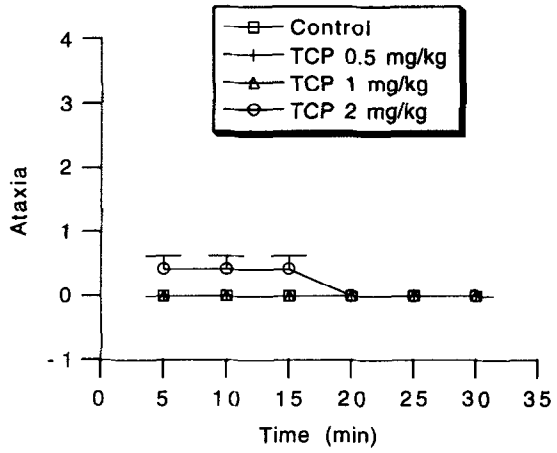

FIG. 2. Evolution of the ataxia degree for control and TCP-treated rats. (The degree of ataxia was noted according to a scale derived from Sturgeon et al.).

the Newman-Keuls test. Because of a nonhomogeneity of the variances, the effects on ataxia were analyzed by a Mann-Whitney *U*-test and the effects of drugs on daily performance during task acquisition in the water maze were calculated by Kruskal-Wallis analysis followed by Friedman test. Spatial probe trial data were analyzed by a chi-square test. Significance was set to $p < 0.05$.

RESULTS

Open Field

The mean ataxia was 1.36 for 0.1 mg/kg MK-801 and 1.6 for 0.2 mg/kg MK-801 (Fig. 1). The difference between these groups and the 0.05-mg/kg MK-801 and control groups (ataxia = 0 for the two groups) was significant ($p < 0.05$; Mann-Whitney *U*-test).

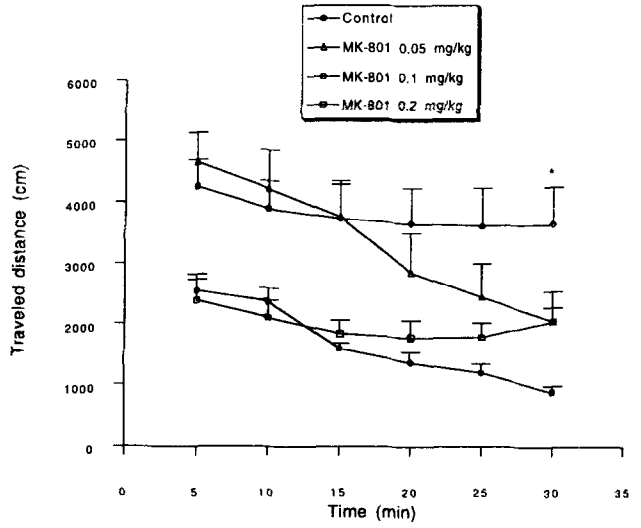

FIG. 3. Distance traveled in the open field by control and MK-801-treated rats. Values represent the mean + SEM for each group. *$p < 0.05$, significantly different from the control group (Newman-Keuls test, $n = 7$ for each group).

TABLE 1

DISTANCE TRAVELED IN THE OPEN FIELD BY CONTROL AND MK-801 TREATED RATS

	Control	MK-801 0.05 mg/kg	MK-801 0.1 mg/kg	MK-801 0.2 mg/kg
Distance traveled(cm)	9,981	20,018*	22,787†	11,976

$n = 7$ for each group.

†Significantly different from control and 0.2-mg/kg group ($p < 0.05$, Newman-Keuls test).

*Significantly different from control group ($p < 0.05$, Newman-Keuls test).

The mean ataxia was 0.21 for 2 mg/kg TCP and 0 for the three other groups (Fig. 2). This difference was not significant.

The evolution of the distance traveled by 5-min phases (Fig. 3) shows that MK-801 induced a hyperactivity but only the difference between the 0.1-mg/kg and the control group was significant for the last 5-min phase ($p < 0.05$, Newman-Keuls test). For the total distance traveled (Table 1), there was a significant difference between the 0.1-mg/kg MK-801 and the 0.2-mg/kg and control groups and between the 0.05-mg/kg and the control group ($p < 0.05$, Newman-Keuls test).

For the TCP, there was not any significant difference between the groups (Fig. 4, Table 2).

Water Maze Acquisition

The escape latencies for MK-801 are shown in Fig. 5. There was a main effect of the time: the Friedman test shows that the group treated with 0.2 mg/kg MK-801 did not acquire the platform location, but the other groups did, with a significant difference appearing from the fourth day. There was also a main effect of treatment: a significant difference between the 0.2-mg/kg MK-801 and the three other groups appears from the fourth day.

The escape latencies for TCP are shown in Fig. 6. There was a main effect of the time: the Friedman test shows that the

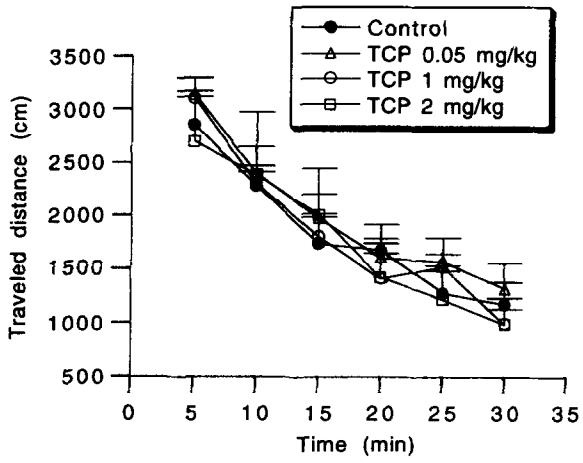

FIG. 4. Distance traveled in the open field by control and TCP-treated rats. Values represent the mean + SEM for each group ($n = 7$ for each group).

TABLE 2
DISTANCE TRAVELED IN THE OPEN FIELD BY CONTROL AND TCP-TREATED RATS

	Control	TCP 0.5 mg/kg	TCP 1 mg/kg	TCP 2 mg/kg
Distance traveled(cm)	11,022	12,048	11,153	10,758

n = 7 for each group.

group treated with 2 mg/kg TCP did not acquire the platform location, but the other groups did, with a significant difference appearing from the fourth day. There was also a main effect of treatment: a significant difference between the 2-mg/kg TCP and the three other groups appears from the fourth day.

Water Maze Spatial Probe Trial

Figure 7 shows the results of the spatial probe trial for MK-801. Control and MK-801 0.05 mg/kg-treated rats swam preferentially in quadrant 1, where the platform was previously placed during the training, rather than in the other three remaining quadrants. Rats treated with 0.1 or 0.2 mg/kg MK-801 did not swim preferentially in quadrant 1, the latter group swiming preferentialy in quadrant 3. Figure 8 shows the results of the spatial probe trial for TCP. Control and TCP 0.5 and 1 mg/kg-treated rats swam preferentially in quadrant 1. Rats treated with 2 mg/kg TCP swam preferentially in quadrant 3.

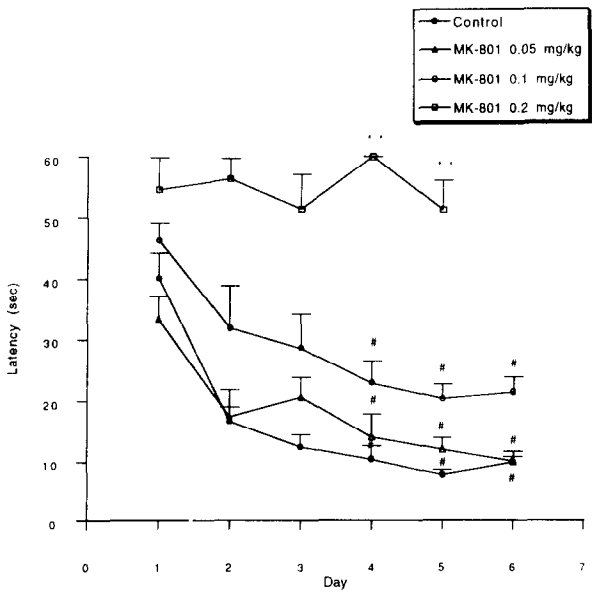

FIG. 5. Escape latency for control and MK-801-treated rats. Values represent the mean + SEM for each group. $**p < 0.01$, significantly different from the three other groups (Friedman test). $\#p < 0.05$, significantly different from the beginning of the test (Friedman test) (n = 7 for each group).

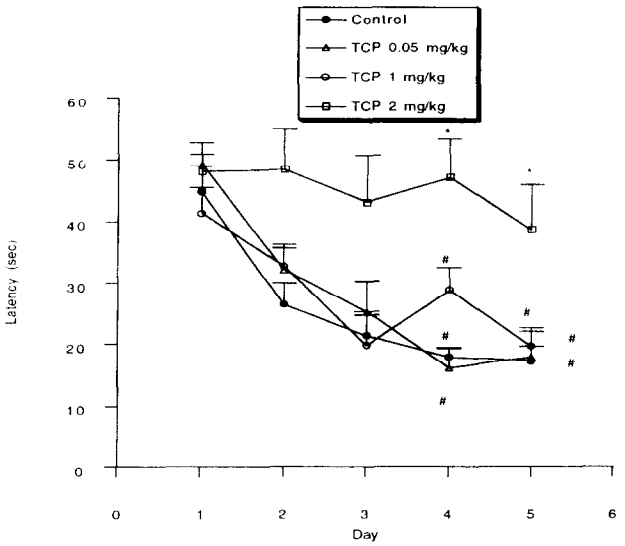

FIG. 6. Escape latency for control and TCP-treated rats. Values represent the mean + SEM for each group (n = 7 for each group). $*p < 05$, significantly different from the three other groups (Friedman test). $\#p < 0.05$, significantly different from the beginning of the test (Friedman test) (n = 7 for each group).

DISCUSSION

In the open field, an ataxia is noted for 0.1 mg/kg MK-801 and a hyperlocomotion for 0.05 and for 0.1 mg/kg, which is in accordance with previous data (41,43), but not for 0.2 mg/kg. In a previous study, Hiramatsu et al. (14) showed that the highest dose of MK-801 induced an ataxia that prevented forward locomotion. In our study, the ataxia is maximum for 0.2 mg/kg MK-801 and is probably responsible of this disappearence of the hyperlocomotion.

The results of the open field concerning TCP show that the

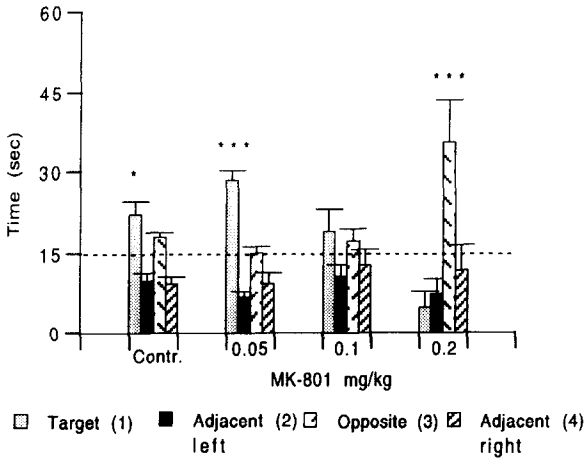

FIG. 7. Swimming time of control and MK-801-treated rats in each of the quadrants of the pool without a platform. Horizontal line represents the chance level (15 s). Values represent the mean + SEM for each group. $*p < 0.05$ and $***p < 0.001$, significantly different from chance level (chi-square test, n = 7 for each group).

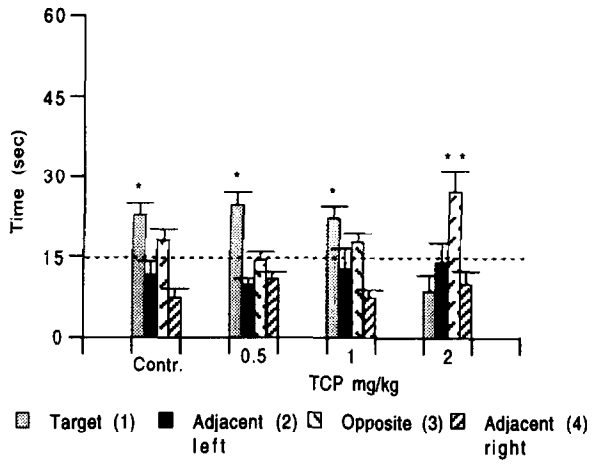

FIG. 8. Swimming time of control and TCP-treated rats in each of the quadrants of the pool without a platform. Horizontal line represents the chance level (15 s). Values represent the mean + SEM for each group. $*p < 0.05$ and $**p < 0.01$, significantly different from chance level (chi-square test, $n = 7$ for each group).

ataxia degree and the distance travelled do not differ from one group to another. From 30 min following the injection of TCP (0.5, 1, or 2 mg/kg, IP), no locomotor effects were observed. In a previous study, Tricklebank et al. (41) assessed the locomotor effects of an IV injection of TCP in mice. These authors described hyperlocomotion, significant from 0.5 mg/kg, and significant ataxia from 1 mg/kg. Although these differences may be explained by differences in route of administration or animal species, a third explanation seems more reasonable: difference in the timing of the measure; Tricklebank et al. analyzed the locomotor parameters only from 5 to 30 min after injection. Accordingly, in our case, we also observed, without quantification, that the rats treated with TCP 1 and 2 mg/kg presented hyperlocomotion and ataxia starting only a few minutes after the injection. However, this symptomatology was transient and lasted about 10–20 min after the injection. It thus appears that, in our experimental conditions, TCP-treated rats did not present locomotor effects 30 min after treatment.

The results of the escape latencies of the control or MK-801-treated rats show that the control group and the 0.05-mg/kg MK-801 group have the same pattern; this is confirmed by the fact that, during the spatial probe trial, they swam preferentialy in the quadrant where the platform had been located. Thus, there was no memory impairment with 0.05 mg/kg MK-801. The results of latency to escape concerning the 0.1 mg/kg MK-801 group suggest that their pattern is similar to that of the control and the 0.05-mg/kg group. However, as shown in Fig. 7, they did not manifest a bias for the target quadrant, proving that they did not really know where the platform was located in the pool. It is likely that they use response (praxis) strategies in which they move according to a specific sequence of movements (28,44). Nevertheless, these strategies are less efficient, because their performance (in terms of escape latency) was lower than that of the 0.05-mg/kg and the control groups (Fig. 5). For the 0.2-mg/kg MK-801 group, the data of the escape latency and the lack of bias for the target quadrant in the spatial probe test all show that these animals did not learn the task. Our results are in agreement with previous studies (17,35).

The evolution of the time taken by the control or TCP-treated rats to locate the platform and the results of the spatial probe test are in total agreement. Indeed, the animals of the control, 0.5- and 1-mg/kg TCP groups had knowledge of the submerged platform location and there was no difference (in terms of escape latency) between the three groups. On the other hand, rats injected with the maximal dose (2 mg/kg) failed to learn the position of the platform.

In conclusion, it appears that, at the two highest doses used, TCP and MK-801 have the same impairment on spatial memory. However, at the minimal therapeutic dose effective against chemically induced seizures (0.1 mg/kg for MK-801 and 1 mg/kg for TCP), TCP, contrary to MK-801, does not induce any memory impairment. Furthermore, at all the doses used, TCP, in contrast to MK-801, presents the particularity that its locomotor side effects are not long lasting, being no longer observed from 30 min after the injection.

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