Chapter 6
Behavioral and Cognitive Impairments Induced by Low Doses of MK-801 and Ketamine

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Abstract N-methyl-D-aspartate receptors (NMDARs) are ionotropic glutamate receptors with a key role in behavioral and cognitive processes. Disruption of NMDARs has traditionally been linked to several neurological disorders, including schizophrenia. NMDAR antagonists can be used as experimental models of symptoms associated with the neural disorders caused by NMDAR dysfunctions, as well as in preclinical studies, to evaluate the effectiveness of potential antipsychotic drugs or cognitive enhancers. The effects of low doses (0.05, 0.1, and 0.2 mg/kg) of MK-801 (a noncompetitive NMDAR antagonist) on motor and cognitive functions were assessed in adult mice. The three doses increased motor activities and evoked inverted-U prepulse inhibition changes, but only the two higher doses impaired associative learning, therefore allowing its application in preclinical studies of cognitive-related deficits. In addition, this study was aimed at determining the motor and behavioral effects produced by subanesthetic doses of ketamine (a non-specific NMDA antagonist) in adult mice and the possibility of generating a mild cognitive impairment model for pharmacological purposes. We evaluated how low doses (10, 15, and 20 mg/kg) of ketamine affected the acquisition of an instrumental conditioning task, as well as their effects on motor and prepulse inhibition capabilities. Results of ketamine administration indicate a clear dose-dependent decrease of learning abilities and motor and prepulse inhibitory effects at the highest dose. Thus, ketamine administration at these three doses can be used as a model of cognitive impairment and for the induction of schizophrenic symptoms.

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The use of these two drugs at low doses in experimental models of selected cognitive disorders is discussed.

Keywords Cognitive functions · Ketamine · MK-801 · Motor activities · NMDA receptors · Operant conditioning · Prepulse inhibition · Schizophrenia

6.1 I ntroduction

NMDARs are a specific type of ionotropic glutamate receptor with key roles in the development of the central nervous system as well as in many different higher functions such as locomotion, learning, and memory [1]. Disruptions in the level or function of NMDARs have traditionally been linked to several neurological and cognitive-related disorders, including schizophrenia and other psychoses [2]. Research on drugs that specifically act on these receptors has grown considerably over the last few decades, mostly aimed at putative treatments of related disorders.

In contrast, the attractiveness of NMDAR antagonists is based firstly on their application as models of symptoms more or less related to neurological disorders caused by NMDAR dysfunctions. Indeed, there is a possibility of using them in preclinical studies, thus allowing the evaluation of the effectiveness of potential antipsychotics and/or cognitive enhancers which would reverse the transient effects induced by the antagonist.

MK-801 is a noncompetitive antagonist of NMDARs with a high affinity and selectivity for a site located in the NMDA channel [3]. Our aim was using this drug at doses lower than those evoking ataxic disorders, noticeable derangements of learning and memory capabilities, and even neural lesions [4]. Because of its interactions with NMDA and dopamine receptor functions at prefrontal and striatal levels, MK-801 could represent an interesting experimental model for the study of higher cognitive functions [5]. It has already been reported that MK-801 administered at doses >0.05 mg/kg in mice evokes overt behavioral and cognitive deficits [6]. In this regard, we have checked here the effects of very low doses of MK-801 (<0.2 mg/kg) on selective motor (open-field), behavioral (prepulse inhibition), and cognitive (operant conditioning) functions.

Ketamine is a hypnotic, analgesic, and amnesic substance usually considered as a dissociative anesthetic [7]. Used at anesthetic doses, ketamine induces a dissociative or cataleptic state characterized by analgesia, amnesia, and changes in the attentional state, but not necessarily loss of consciousness [8]. Ketamine is an antagonist of NMDA receptors but also of non-glutamatergic (muscarinic, opioid) receptors [7]. Administered at subanesthetic doses, ketamine can evoke psycho-dyslectic and psychotic symptoms. We consider that it would be interesting to study in detail the motor, behavioral, and cognitive effects of the administration of subanesthetic doses (≤20 mg/kg) of ketamine to determine whether this procedure can be used as an experimental model of cognitive disorders, including schizophrenia and other related psychiatric disorders.

6.2 Methods

6.2.1 Experimental Animals

Experiments were carried out in a total of 80 C57Bl/6 male adult mice (3–5 months old; 25–30 g) obtained from an official supplier (University of Granada Animal House, Granada, Spain). Upon arrival, animals were housed in separate cages ($n = 5$ per cage), but they were switched to individual cages 1 week before the beginning of the experimental study. Mice were kept on a 12-h light/dark cycle with constant ambient temperature (21.5 ± 1 °C) and humidity (55 ± 8%). Food and water were available ad libitum, except for the operant conditioning procedures. Experiments were carried out in accordance with the guidelines of the European Union (2010/63/EU) and Spanish regulations (BOE 34/11370-421, 2013) for the use of laboratory animals in chronic studies. All experimental protocols were also approved by the local Ethics Committee.

Animals were divided in eight experimental groups ($n = 10$ animals/group). In the case of MK-801, we prepared a control (saline) group and three experimental groups with increasing (0.05, 0.1, and 0.2 mg/kg) doses of the drug dissolved in saline. For ketamine, we prepared a control (saline) group and three experimental groups with increasing (10, 15, and 20 mg/kg) doses of the drug.

6.2.2 Open-Field Test

As illustrated in Fig. 6.1a, mice were placed in the center of the open-field apparatus (a box of 28 × 28 × 21 cm from Cibertec S.A., Madrid, Spain) and observed for 15 min. The apparatus was provided with infrared lights, located every 2 cm, in the three (X, Y, Z) spatial axes. Animals' displacements in the open field were quantified automatically with the help of a computer program (MUX_XYZ16L), also from Cibertec S.A. The apparatus was located in a soundproof room, and the experimental area was dimly and homogeneously illuminated. In order to avoid any interference with the following experimental animal, the whole apparatus was cleaned with alcohol (70° proof) after each use.

6.2.3 Prepulse Inhibition Task

Animals were placed individually inside a startle chamber (Cibertec S.A.; Fig. 6.2a–c). The startle response was measured using a piezoelectric accelerometer controlled by a computer, using the protocol described elsewhere [9, 10]. The digitized signal was averaged from 25 to 30 recordings. For training, the mouse was placed in the startle chamber for an acclimation period of 3 min.

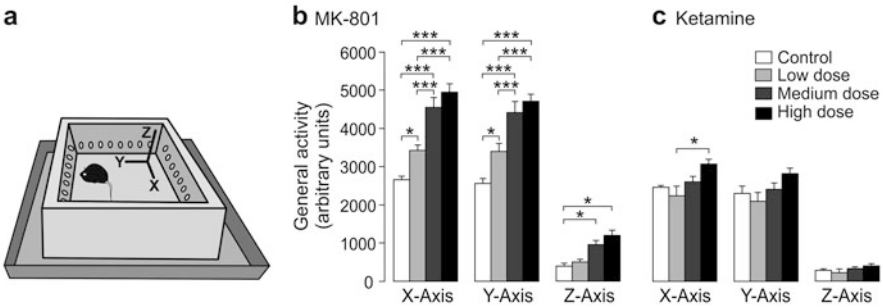

Fig. 6.1 Effects of MK-801 and ketamine administration on motor activities performed by adult mice in an open field. (**a**) A diagram of the open field. The recording area was provided by infrared lights (2 cm apart) in the three axes (X, Y, and Z). (**b**) Results collected from the four groups of MK-801 animals for the three spatial axes. Note the significant increase in motor activity induced by the three selected doses of MK-801. (**c**) The same for the four groups of ketamine mice. Values are Mean ± SEM of the collected data. *$p < 0.05$; ***$p < 0.001$

Baseline responses were averaged after the presentation of 20 sounds (125 dB, 100 ms long). During prepulse inhibition trials, the same 125-dB 100-ms burst was preceded (250 ms) by a prepulse stimulus of 85 dB, lasting for 50 ms. Trials including prepulse stimuli were randomly presented with normal startle stimuli, the final total being 25 of each. The ambient background noise was 70 dB. The total startle response area (mV × ms) was recorded and quantified. Following [11], data were computed in accordance with the Eq. (6.1):

$$\left[(\text{startle/prepulse ratio}) \times 100\right] / \text{baseline value.} \tag{6.1}$$

6.2.4 Operant Conditioning Procedures

Following previous descriptions by [12, 13], operant conditioning took place in five Skinner box modules measuring 12.5 × 13.5 × 18.5 cm (MED Associates, St. Albans, VT, USA; Fig. 6.3a). Each Skinner box was housed within a sound-attenuating chamber (90 × 55 × 60 cm), which was constantly illuminated (19 W lamp) and exposed to a 45 dB white noise (Cibertec S.A.). Each Skinner box was equipped with a food dispenser from which pellets (MLabRodent Tablet, 20 mg; Test Diet, Richmond, IN, USA) could be delivered by pressing a lever. Before training, mice were handled daily for 7 days and food-deprived to 85–90% of their free-feeding weight.

For operant conditioning, animals were trained to press the lever to receive pellets from the feeder using a fixed-ratio (1:1) schedule (Fig. 6.3b). Sessions lasted for 20 min. Animals were maintained on this 1:1 schedule until they reached

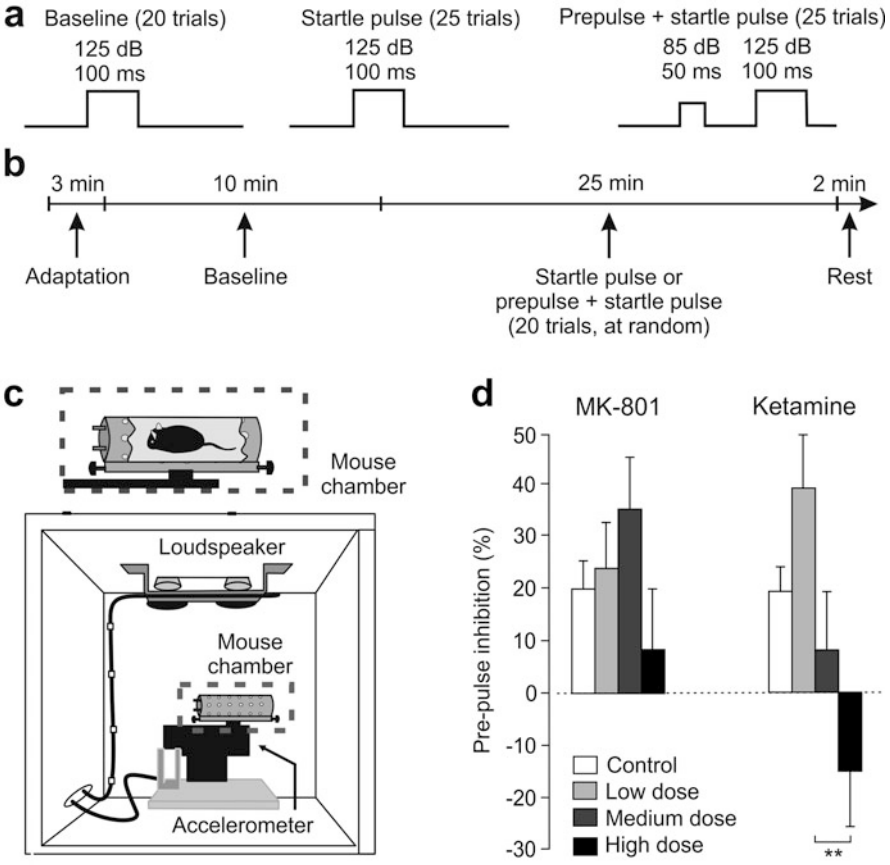

Fig. 6.2 Effects of MK-801 and ketamine administration on the execution of the acoustic startle response and prepulse inhibition test by adult mice. (**a**) The three types of tone used in this study. (**b**) Experimental design of the startle response and prepulse inhibition test. (**c**) Startle chamber. (**d**) Graphical representation of the prepulse inhibition (% of the startle response) obtained from the four MK-801 and ketamine groups. Values are Mean ± SEM of the collected data. $^{**}p < 0.01$

the selected criterion—namely, until they were able to obtain ≥20 pellets/session for two successive sessions. With these experimental procedures, wild-type mice reached criterion after 4–7 days of training [14].

Once criterion was reached, animals were further conditioned using a light/dark protocol for 10 additional days (Fig. 6.3c). In this protocol, only lever presses during the light period (20 s) were reinforced with a pellet. Lever presses performed during the dark period (20 ± 10 s) were not reinforced but restarted the dark protocol for an additional random (1–10 s) time.

The number of lever presses during light and dark periods was quantified for each training session. Conditioning programs, lever presses, and delivered reinforcements were monitored and recorded by a computer, using a MED-PC program (MED Associates, St. Albans, VT, USA).

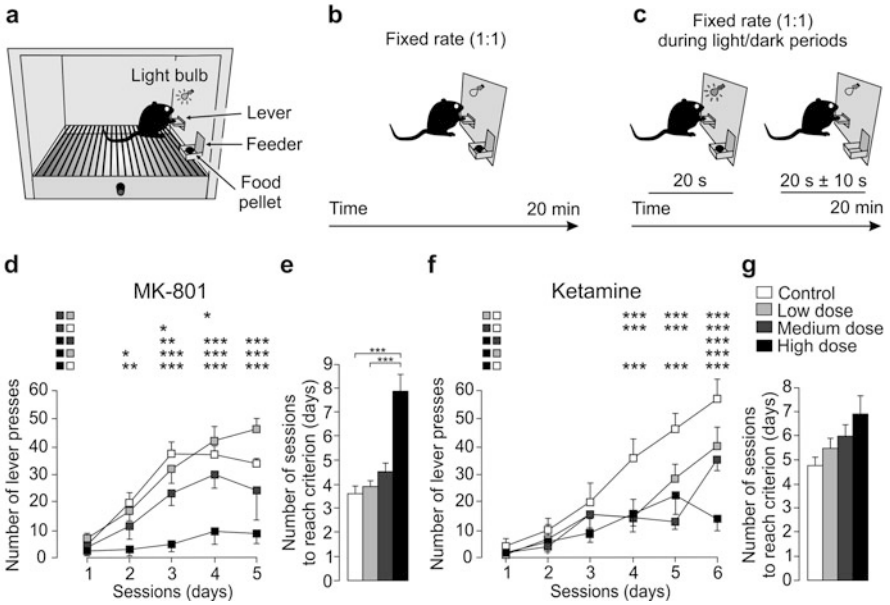

Fig. 6.3 Effects of MK-801 and ketamine administration on the execution of an operant conditioning task using a fixed-ratio (1:1) schedule. (**a**–**c**) Mice were trained in a Skinner box to press a lever to obtain a food pellet (**a**). For operant conditioning, we used two paradigms of increasing difficulty. In the first paradigm (a fixed-ratio of 1:1), the selected criterion was that the mouse had to press the lever 20 times per 20 min session for 2 successive sessions to successfully complete the task (**b**). In the second paradigm (a fixed-ratio of 1:1 during light/dark periods), lever presses were rewarded only when a light bulb was switched on. In this case, lever presses while the bulb was off were punished with a time penalty of up to 10 s during which the bulb would not turn on (**c**). (**d** and **e**) Performance of mice during the first 5 days of training with the fixed-ratio (1:1) schedule and following the administration of the three selected doses of MK-801. Significant differences between groups are indicated (**d**). Days to reach the selected criterion by each experimental group are illustrated in (**e**). (**f** and **g**) Same as in (**d** and **e**) but for data collected from mice injected with the three selected doses of ketamine. The code for the four experimental groups in (**g**) is also for (**d**–**f**). $*p < 0.05$; $**p < 0.01$; $***p < 0.001$

6.2.5 Drug Administration

(+)-MK-801 (Dizocilpine, Sigma-Aldrich, Steinheim, Germany) was dissolved in a 0.9% NaCl solution and administered i.p. in a total volume of 0.3 mL/mouse. The selected doses were 0.05 mg/kg, 0.1 mg/kg, and 0.2 mg/kg [6]. Ketamine [(2R)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone; Sigma-Aldrich, Steinheim, Germany] was dissolved in a 0.9% NaCl solution and administered i.p. in a total volume of 0.3 mL/mouse. The respective control groups were injected with the saline solution at the indicated volume. The selected doses were 10 mg/kg, 15 mg/kg, and 20 mg/kg. Drugs were administered 30 min before the performance of the selected test.

6.2.6 Data Analysis

Collected data were translated into Excel spreadsheets for further analysis and representation. Unless otherwise indicated, data are represented as mean ± SEM. Statistical analyses were carried out with the help of the SigmaPlot 11.0 program (Systat Software Inc., San Jose, CA, USA). Acquired data from the open field and the startle chamber were analyzed using one-way repeated measures ANOVA with all pairwise multiple comparison procedures (Holm-Sidak method) when statistical differences were found. Kruskal-Wallis one-way ANOVA on ranks was used when the normality test or the equal variance test failed. Data from the operant conditioning test were analyzed using two-way repeated measures ANOVA, with the Kruskal-Wallis-Tukey test and the Holm-Sidak method as needed. Data collected from the light/dark test were analyzed with linear regression lines. The linear equation and coefficient of correlation corresponding to each set of data were calculated.

6.3 Results

6.3.1 Performance of the Open-Field Test by Mice Treated with MK-801 and Ketamine

As described in Methods, animals of each group were placed individually in an open-field apparatus (Fig. 6.1a) to determine their motor activities for a single 15-min period. The number of light-beam crossings in the three spatial axes (X, Y, Z) was quantified and totalized for each experimental group. The administration of increasing doses of MK-801 significantly increased the spontaneous motor activities of the experimental animals in the three axes (X, $F_{[3, 36]} = 25.55$, $p < 0.001$; Y, $F_{[3, 36]} = 23.44$, $p < 0.001$; and Z, $H = 16.48$ with three degrees of freedom, $p < 0.05$). In contrast, the administration of the selected doses of ketamine evoked no significantly different motor activities in the open field, apart from the highest dose (20 mg/kg) and only for the X-axis ($F_{[3, 36]} = 3.33$, $p < 0.05$).

On the whole, the selected doses of MK-801, but not those of ketamine, produced an evident increase in the motor activity of the animals in the open field, suggesting an increase in their exploratory behaviors.

6.3.2 Prepulse Inhibition of the Startle Response by Mice Treated with MK-801 and Ketamine

In Fig. 6.2a–c is illustrated the apparatus used to evoke a startle response in individual mice and the protocol followed to evoke its inhibition. The startle response was evoked by the presentation of a 125-dB 100-ms tone, while its

inhibition was achieved by the presentation of an 85-dB 50-ms tone 250 ms in advance of the stronger tone. The administration of increasing doses of MK-801 evoked an inverted-U modification of the prepulse inhibition obtained in the control group (Fig. 6.2d). However, the collected results did not reach significant differences. In contrast, the highest (20 mg/kg) dose of ketamine used in these experiments produced a significant decrease in the evoked prepulse inhibition. In conclusion, only the highest dose of ketamine evoked a significant decrease in the amount of prepulse inhibition of the startle response reached by the control groups.

6.3.3 Operant Conditioning of Animals Treated with MK-801 and Ketamine

Mice were trained in Skinner boxes to obtain a food pellet every time they pressed a lever in daily sessions of 20 min, using a fixed-ratio (1:1) schedule (Fig. 6.3a, b). Mice were considered to complete the task when pressing the lever ≥20 times in 2 successive sessions (i.e., the criterion; Fig. 6.3d–g). As shown in Fig. 6.3d, the administration of increasing doses of MK-801 significantly ($F_{[12,144]} = 6.06$, $p < 0.001$) affected the animals' proper performance of the operant conditioning task, particularly for mice administered with the highest dose (0.2 mg/kg).

In addition, control MK-801 mice and those receiving the two lower doses (0.05 and 0.1 mg/kg) reached the selected criterion in ≈4 days, but those injected with the highest dose (0.2 mg/kg) reached criterion significantly later ($p < 0.001$; $H = 21.39$ with three degrees of freedom; Fig. 6.3e). The administration of increasing doses of ketamine also significantly ($F_{[15,180]} = 5.08$, $p < 0.001$) decreased performance of the mice in the Skinner box during the first six training sessions (Fig. 6.3f).

Although the administration of increasing doses of ketamine increased the number of sessions necessary to reach the selected criterion, no significant differences between groups were observed ($p = 0.9092$; $H = 6.45$ with three degrees of freedom; Fig. 6.3g).

Mice that successfully reached the above criterion were subjected to a more complex operant conditioning task. In this case, pressing the lever was rewarded with a food pellet only during periods of 20 s in which a light bulb above the lever was switched on (light/dark, Fig. 6.3c). As illustrated in Fig. 6.4a, control MK-801 decreased the number of lever presses during the dark periods across the ten training sessions. In contrast, the administration of increasing doses of MK-801 prevented the proper acquisition of this operant conditioning task (Fig. 6.4b, c) and even reversed it (Fig. 6.4d). In the same way, the administration of the highest dose of ketamine disturbed the proper acquisition of the light/dark task (Fig. 6.4e–h).

In summary, the administration of low doses of MK-801 and ketamine affected the proper acquisition of an operant conditioning task, mainly for the MK-801 and ketamine groups administered the highest doses (0.2 mg/kg and 20 mg/kg,

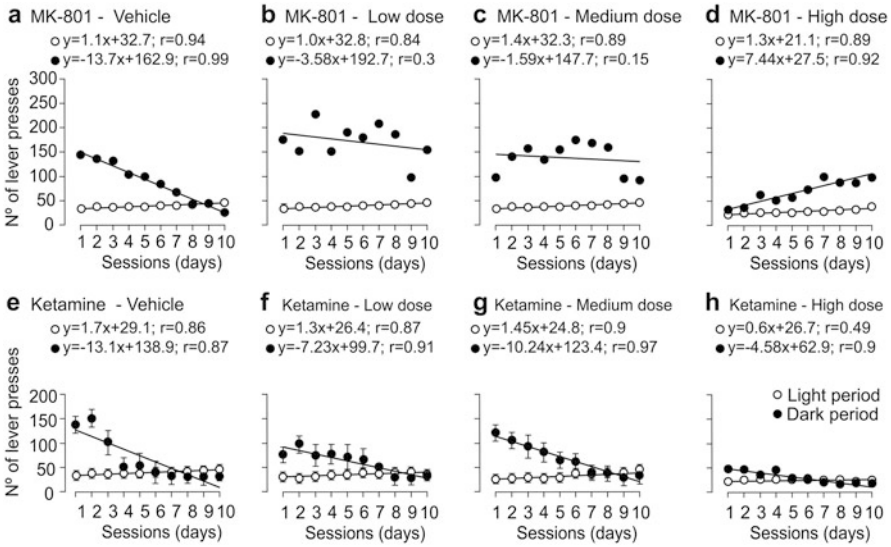

Fig. 6.4 Effects of MK-801 and ketamine administration on the execution of an operant conditioning task using a fixed-ratio (1:1) schedule in a go/non-go situation. In this situation, only lever presses carried out during the light period were rewarded. Lever presses carried out while the bulb was off were punished with up to 10 additional seconds during which the bulb would not turn on (light/dark paradigm; see Fig. 6.3c). (**a–d**) Lever presses performed by mice of the four (control and three doses) MK-801 groups across ten successive sessions using the light/dark paradigm. (**e–h**) Same for experiments carried out with the four ketamine groups. As indicated in (**h**): white circles, lever presses when the light bulb was on (light); black circles, lever presses when the bulb was off (dark). Regression lines and their coefficient of correlation (*r*) are indicated above each representation

respectively). The three groups administered with MK-801 and the ketamine group administered with the highest dose were unable to acquire an operant light/dark task entailing the specific inhibition of natural appetitive behaviors.

6.4 Discussion

We have studied here the effects of low doses of MK-801 and of ketamine on the spontaneous motor activities, prepulse inhibition of a tone-evoked startle response, and associative learning capabilities of young adult mice. The aim was to determine whether those drugs, administered at low doses, could evoke symptoms related with cognition-related disorders such as schizophrenia and related psychoses.

The three doses of MK-801 used here evoked significant increases in the motor activities of the experimental animals in the open-field apparatus. It can be proposed that this increase in exploratory activities also disturbed the proper acquisition of the

light/dark operant conditioning task presented by the three groups of mice injected with MK-801, particularly those administered with the highest dose.

As already described [15], mice injected with the highest dose used here (0.2 mg/kg) presented evident motor deficits (such as ataxic movements, vestibular misbalances, etc.); these motor effects could rule out using this dose for operant conditioning tasks. Finally, we have been unable to reproduce here the effects of MK-801 on prepulse inhibition described elsewhere [16].

According to the present results, ketamine administration at subanesthetic doses did not evoke the noticeable hyperactive motor responses described in mice following the acute administration of a much higher dose (100 mg/kg, i.p.) [17]. However, the highest dose of ketamine used here (20 mg/kg) significantly increased motor activities in the open field and decreased the inhibitory effects of a prepulse on the tone-evoked startle response but did not prevent the proper acquisition of an operant conditioning task. In this sense, this low dose of ketamine can be used to evoke mild cognitive impairments potentially related to some psychotic states. For example, it is well known that the absence of a proper prepulse inhibition mechanism is considered a symptom related to a schizophrenic condition [9, 18, 19].

The administration of low doses ($\leq$12 mg/kg) of ketamine also disturbed the acquisition of an instrumental conditioning in rats, using fixed-interval (1:50 s and 1:200 s) schedules [20]. In this regard, it is possible that a fixed interval could represent a task more difficult to acquire than the fixed-ratio (1:1) schedule used here.

In conclusion, the highest dose of MK-801 used here could be a useful experimental tool for evoking cognitive-related impairments involving operant conditioning tasks, probably related to the increase in interspecific exploratory activities. Similarly, the highest dose of ketamine used here could be useful for creating deficits in the prepulse inhibition test.

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