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Activities of the Antipsychotic Drugs Haloperidol and Risperidone on Behavioural Effects Induced by Ketamine in Mice

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Abstract

This study presents the actions of risperidone (Risp) and haloperidol (Hal) on the behavioral effects elicited by ketamine (Ket) on open-field (OF), rota rod (RR) and tail suspension (TS) tests in mice. Male Swiss albino mice (25–30g) were used. Antipsychotics were administered alone (Risp: 0.1 or 0.2 mg/kg, ip; Hal: 0.1 and 0.2 mg/kg, ip) or thirty minutes before Ket (10 mg/Kg, ip). Ket increased (Ket: 63.3 ± 4.2) the locomotor activity compared to control, while neuroleptics decreased it (25.5 ± 4.2). Pretreatment with neuroleptics, in both doses, blocked hyperlocomotion caused by Ket. In RR, Ket decreased (Ket: 15 ± 4.1) the permanence time of the animals compared to control (Control: 59 ± 0.6), but this effect was not observed when neuroleptics were administered alone. Pretreatment with neuroleptics reverted the effect of Ket only in the RR. While Ket (17.3 ± 5.6) decreased the time of immobility in the tail suspension test compared to the control (80.2 ± 10.2), the pretreatment with neuroleptics reverted this mobility. The action of neuroleptics in this model made possible

the blockade of the effects caused by acute administration of Ket. Thus, the mechanism of action of ketamine may involve the dopaminergic system.

Keywords

Antipsychotic drug • Ketamine • Locomotor activity • Schizophrenia

Introduction

Schizophrenia is a heterogeneous syndrome with no pathognomonic features that commonly begins in late adolescence. The syndrome has a poor outcome and is present in 0.85% of individuals worldwide [1]. There are many theories attempting to explain the physiopathology of this illness, including the dopamine hypothesis. This hypothesis postulates that the dopaminergic hyperfunction is based on the following evidences: 1) psychotic symptoms presented by patients using drugs that induce dopamine release; 2) efficacy of typical antipsychotics in many patients [2] via action on dopamine D_2-like receptors [3, 4]. However, the basis of the dopaminergic hypothesis has been questioned in some studies which demonstrated that a certain level (> 65%) of receptor blockade is necessary [5, 6], but not sufficient to cause clinical results [3]. Some atypical antipsychotics are efficient in the schizophrenia treatment, although they block a lower number of dopamine receptors (< 60%) [7, 8].

The glutamate model, however, became more accepted in the late 1980s [9]. Current researches have indicated that dysfunctions in the neurotransmission modulated by the excitatory amino acid glutamate may play a central role in the physiopathology of schizophrenia [10]. The glutamatergic system has several receptors that are activated by glutamate [11]. Among these, the N-methyl-D-aspartate (NMDA) receptors are especially important for the understanding of the illness [3].

Ketamine is one derivative of the phencyclidine hydrochloride (PCP) [12]. It is referred in literature as a dissociative anesthetic, since it induces strong sensory loss and analgesia, as well as amnesia and paralysis, without real loss of consciousness [13]. Ketamine, a competitive antagonist of NMDA receptor, induces behavioral effects in healthy humans that mimic positive, negative and cognitive schizophrenic symptoms [14–16]. Schizophrenic patients using ketamine present symptoms similar to that experienced during the active phase of the illness [17–19]. These data provide support for the hypothesis that reduced NMDA receptor function could contribute to the physiopathology of schizophrenia [20].

Antipsychotics or neuroleptics, drugs clinically used for the schizophrenia treatment, are categorized as dopaminergic antagonists, although many also act in other targets, particularly in the serotonin 5-HT_2 receptors [21]. Vasconcelos [22] reported the importance of the establishment of animal models in order to study schizophrenia and possible development of new antipsychotic drugs. The purpose of this work is to understand the interaction between the dopaminergic and glutamatergic systems, analyzing the effects of risperidone (atypical antipsychotic) and haloperidol (typical antipsychotic) in the behavioral model induced by ketamine in mice.

Experimental

Animals

The experiments were carried out on male Swiss albino mice (*Mus musculus)* (25–30 g). They were maintained at a controlled temperature (23 ± 1 °C) with a 12h dark/light cycle and free access to water and food. All the experimental procedures were performed in accordance with the opinion of Local Ethics Committee (N. 07465201-0).

Drugs and treatment

Ketamine hydrochloride (50 mg/mL, ampoules), haloperidol (5 mg/mL, ampoules) and risperidone (1 mg/pill) were used. All drugs were dissolved in distilled water and administered intraperitoneally (ip) in volumes of 10 mL/Kg body weight. Risperidone (0.1 mg/Kg or 0.2 mg/Kg) or haloperidol (0.1 mg/Kg or 0.2 mg/Kg) were administered alone or thirty minutes before ketamine (10 mg/Kg). Control animals received distilled water in the same period.

Procedure

Animals were tested during the light period and observed in a closed room, poorly illuminated, at a constant temperature of 25 ± 1 °C. Immediately after treatment with ketamine or water, the tests were performed. First, animals were placed in the open field arena where the locomotor activities, such as number of grooming, rearing and stereotyped activity (repetitive movements) were measured. Subsequently, the same animals were placed on rota rod and on the tail suspension device straight afterward.

Open-field test (OF)

The OF area was made of acrylic (transparent walls and black floor, 30 cm x 30 cm x 20 cm) divided into nine squares of equal area. The OF was used to evaluate the animals exploratory activity [23]. The observed parameters were: number of squares crossed (with the four paws) during three minutes after one minute for acclimatization (locomotor activity) and number of grooming and rearing. In this apparatus, behavioral changes, such as stereotyped behaviors (striking or perseverative behaviors), walking in circles and ataxia were also observed and recorded.

Rota rod (RR)

The method of Dunham and Miya [24] was used on rota rod test. Animals were placed with the paws on a 2,5 cm diameter bar, 25 cm above the floor, which rotates 12 times per minute. The number of falls (up to three falls) and the time of permanence on the bar for one minute were registered.

Tail suspension test (TS)

For the tail suspension test, the method described by Porsolt et al. [25] was used. Mice were suspended by tail on the edge of a shelf 58 cm above a table top by adhesive tape placed approximately 1 cm from the tip of the tail. The duration of immobility was recorded during a period of five minutes.

Statistical analyses

All analyses were performed using one-way analysis of variance (ANOVA), at Prism 3.0 software. For significant results, multiple comparisons were made using Tukey as the post hoc test. Results were considered significant at $p < 0.05$, and presented as mean ± E.P.M.

Results

Open-field test

The number of crossing was increased by Ketamine (Ket 10mg/Kg: 63.3 ± 4.2) and significantly decreased by haloperidol (Hal 0.1 mg/Kg: 7.38 ± 1.5; Hal 0.2 mg/Kg: 3.5 ± 1.2) and risperidone (Risp 0.1 mg/Kg: 11.4 ± 4.1; Risp 0.2 mg/Kg: 4.2 ± 2) when compared to control (25.5 ± 4.2). The hypermotility (seen using the same parameter) induced by ketamine was significantly decreased by both neuroleptics at all doses of pretreatment [Hal 0.1 mg/Kg + Ket: 5.9 ± 2.8; Halo 0.2 mg/Kg + Ket: 2.2 ± 0.8; Risp 0.1 mg/Kg + Ket: 29.9 ± 6.3; Risp 0.2 mg/Kg + Ket: 2.2 ± 0.8]. However, animals treated with risperidone (0.1 mg/Kg) before injection of Ket reduced their motility to control levels [$F(9,105) = 39.09$; $p < 0001$], as shown in Table 1. Ketamine (Ket: 1.1 ± 0.7) as well as the neuroleptics (Hal 0.1 mg/Kg: 5.1 ± 1.4; Hal 0.2 mg/Kg: 0.7 ± 0.2; Risp 0.1 mg/Kg: 0.7 ± 0.4; Risp 0.2 mg/Kg: 1.6 ± 0.6) decreased the number of rearing compared to control (13.45 ± 1.6) [$F(9,106)= 30.69$; $p < 0001$]. Similar effect was observed when the pretreatment with neuroleptics was performed (Hal + Ket or Risp + Ket). All drugs decreased the number of grooming compared to control (3.3 ± 0.3), except haloperidol (2.3 ± 0.4) at the 0.1 mg/Kg dose [$F(9,107) = 19.26$; $p < 0001$] (Table 1).

Tab. 1. Effects of antipsichotics drugs and ketamine on the open-field test in mice.

Group	Locomotor activity	Rearing	Gromming
Controle	25,5 ± 4,2 (10)	13,45 ± 1,6 (11)	3,3 ± 0,3 (10)
Ket 10	63,3 ± 4,2 (10)[a]	1,1 ± 0,7 (10)[a]	0,2 ± 0,1(10)[a]
Hal 0,1	7,38 ± 1,5 (13)[a,b]	5,1 ± 1,4 (11)[a,b]	2,3 ± 0,4 (11)[b]
Hal 0,1 + Ket	5,9 ± 2,8 (12)[a,b]	0,4 ± 0,3 (12)[a,c]	0,6 ± 0,25 (12)[a,c]
Hal 0,2	3,5 ± 1,2 (12)[a,b]	0,7 ± 0,2 (12)[a,c]	0,6 ± 0,1 (12)[a,c]
Hal 0,2 + Ket	2,2 ± 0,8 (10)[a,b]	0,25 ± 0,2 (12)[a]	0,08 ± 0,08 (12)[a]
Risp 0,1	11,4 ± 4,1(10)[b]	0,7 ± 0,4 (9)[a]	0,6 ± 0,2 (10)[a]
Risp 0,1 + Ket	29,9 ± 6,3 (9)[b,d]	0,0 ± 0 (10)[a]	0,4 ± 0,2 (10)[a]
Risp 0,2	4,2 ± 2 (10)[a,b]	1,6 ± 0,6 (10)[a]	1,2 ± 0,3 (9)[a]
Risp 0,2 + Ket	2,2 ± 0,8 (10)[a,b]	0 ± 0 (10)[a]	0,08 ± 0,08 (12)[a,e]
Risp 0,2 + Ket	2,2 ± 0,8 (10)[a,b]	0 ± 0 (10)[a]	0,08 ± 0,08 (12)[a,e]

Values are reported as means ± e.p.m. for the number of mice shown in parentheses. a, b, c, d and e ($p<0.05$) as compared to control, Ketamine (Ket 10), Hal 0.1, Risp 0.1 and Risp 0.2, respectively. Analysis of variance and Tukey as the post-hoc test.

The behavior effects of ketamine evaluated on the stereotyped activity (Ket: 2.7 ± 0.6, $F(9,99) = 9.299$, $p < 0.0001$), walking in circle (Ket: 3 ± 0.6, $F(9,99) = 12.54$, $p < 0.0001$) and ataxia (Ket: 3.1 ± 1, $F(9,99) = 9.045$, $p < 0.0001$) (Figures 1 and 2) were different from the control (0.0 ± 0.0). Risp (0.1 mg) reversed the stereotyped activity (Risp 0.1 mg/Kg + Ket : 0.2 ± 0.2) (Figure 2A) and ataxia (Risp 0.1 mg/Kg + Ket : 0.3 ± 0.2) (Figure 2C) caused by Ket alone, but did not alter the behavior of walking in circle (Figure 2B).

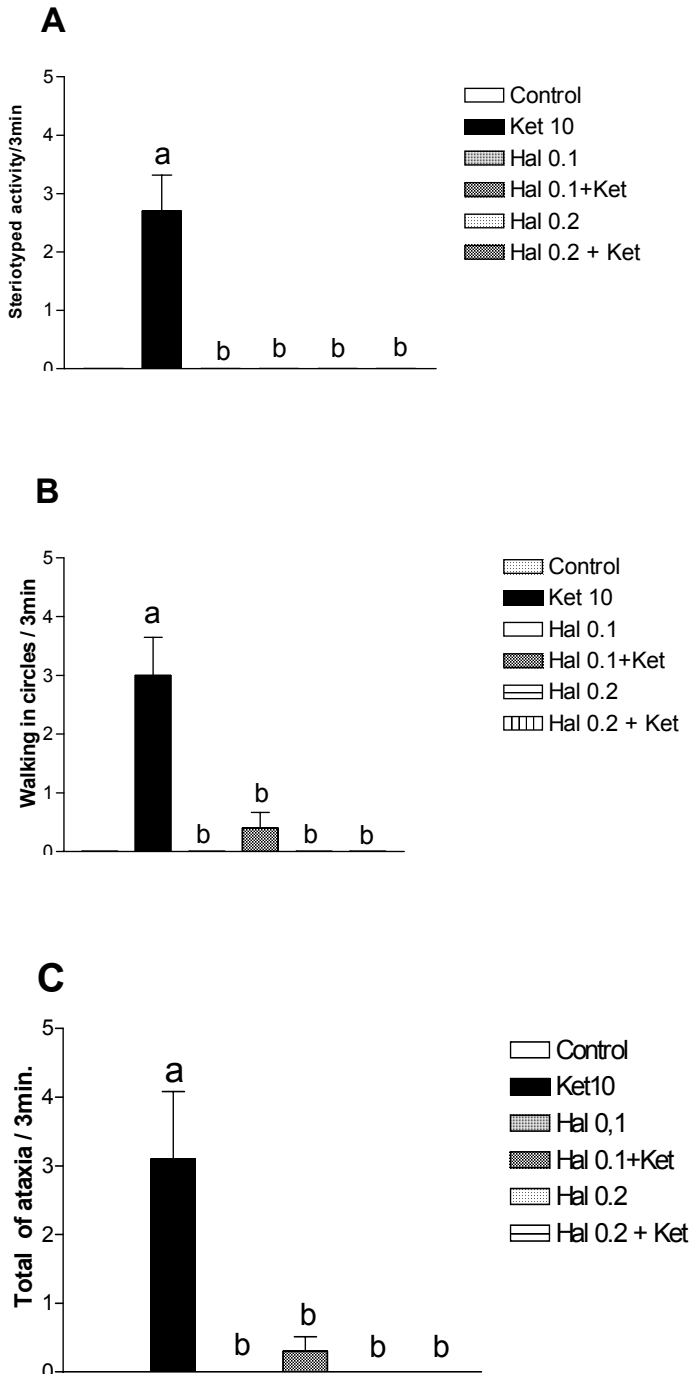

Fig 1. Effects of ketamine and haloperidol on mice behavior: (A) stereotyped activity, (B) walking in circles and (C) ataxia in mice. The figure represents the animals that showed the behaviour on the open field device for three minutes. The results are presented as mean ± EPM. *n* = 10. a and b ($p<0.05$) as compared to control or Ketamine (Ket 10), respectively. Analysis of variance and Tukey as the post-hoc test.

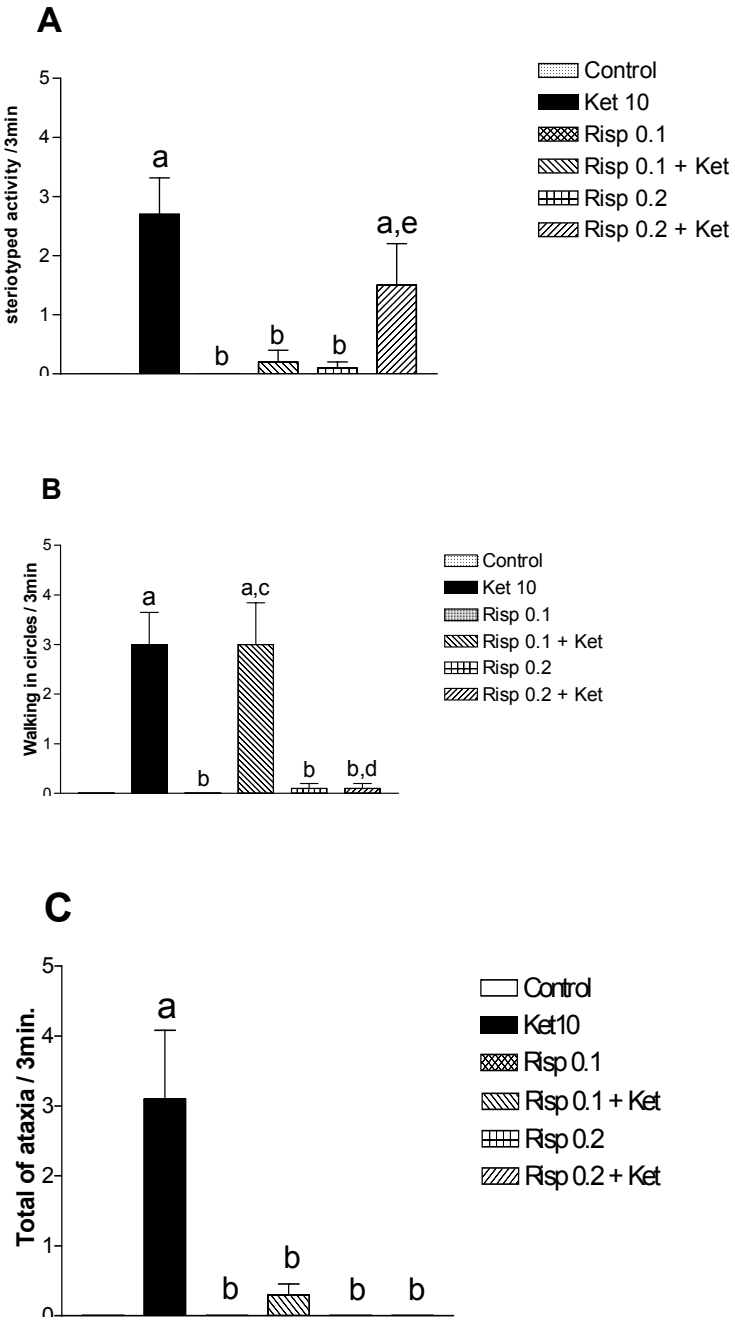

Fig 2. Effects of ketamine and risperidone on mice behavior: (A) stereotyped activity (B) walking in circles, and (C) ataxia in mice. The figure represents the animals that showed the behaviour on the open field device for three min. The results are presented as mean ± EPM. *n* = 10. a, b, c, d and e ($p<0.05$) as compared to control, Ket 10, Risp 0.1, Risp 0.1 + Ket or Risp 0.2, respectively. Analysis of variance and Tukey as the post-hoc test.

Rota rod

At the Rota rod test, ketamine (Ket: 15.06 ± 4.1) significantly decreased the time of animals permanence on the bar compared to control (59.01 ± 0.6) (Table 2). The pretreatment with neuroleptics alone induced no changes. However, animals that received Ketamine after have being treated with haloperidol at 0.2 mg (Hal 0.2 mg/Kg + Ket: 41 ± 5.5) and with risperidone at 0,1 mg (Risp 0.1 mg/Kg + Ket: 42,8 ± 6.3) increased the time of permanence on the bar compared to the Ket alone group [$F(9,110) = 9.101$; $p < 0001$]. Ketamine (Ket: 2.9 ± 0.1) increased the number of falls (Table 2) compared to control (control: 0.14 ± 0.01), and this effect was not changed by the neuroleptic pretreatment [$F(9,120) = 12.15$; $p < 0001$].

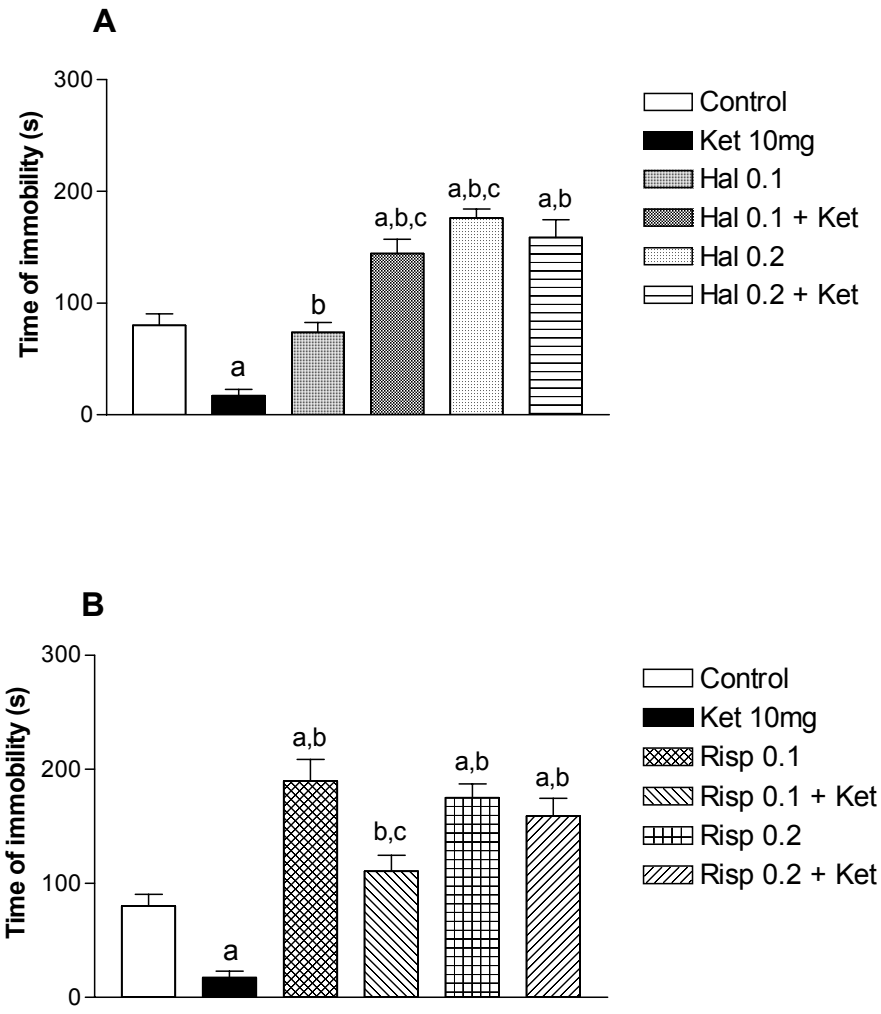

Fig 3. Effects of drugs in the tail suspension test on mice behavior. A - Haloperidol alone and in association with ketamine. B – Risperidone alone and in association with Ketamine. The figure shows the time of immobility in five min. The results are presented as mean ± EPM. (n=10 or 20). a, b and c, ($p<0.05$) as compared to control, Ket 10 and Risp 0.1, respectively. Analysis of variance and Tukey as the post-hoc test.

Tail suspension test (TS)

In TS (figure 3), ketamine (Ket: 17.3 ± 5.6) significantly decreased the time of immobility in mice compared to the control group (80.2 ± 10.2). However, the pretreatment of animals with neuroleptics (risperidone e haloperidol) blocked the effect of ketamine. Haloperidol at the highest dose (Hal 0.2 mg/Kg: 176.1 ±8) and risperidone in the two doses (Risp 0.1 mg/Kg: 189.7 ±19; Risp 0.2 mg/Kg: 175.2 ± 12) significantly increased the time of immobility when compared to control [$F(9,123) = 19.96$; $p < 0001$].

Tab. 2. Effects of antipsichotics drugs and ketamine on the Rota rod test in mice.

Group	Time of permanence (s)	Nº falls
Controle	59,01 ± 0,6 (10)	0,14 ± 0,01 (14)
Ket	15,06 ± 4,1 (10)[a]	2,9 ± 0,1(10)[a]
Hal 0,1	55,06 ± 1,3 (14)[b]	0,86 ± 0,2 (14)[b]
Hal 0,1 + Ket	28,03 ± 5,2 (14)[a,c]	2,6 ± 0,2 (20)[a,c]
Hal 0,2	46 ± 3,7 (12)[b]	1,6 ± 0,3 (12)[a]
Hal 0,2 + Ket	41 ± 5,5 (12)[b]	2,2 ± 0,3 (12)[a]
Risp 0,1	54 ± 1,8 (09)[b]	0,7 ± 0,2 (09)[b]
Risp 0,1 + Ket	42,8 ± 6,3 (10)[b]	1,6 ± 0,5 (10)[a]
Risp 0,2	45,1 ± 4,3 (10)[b]	1,7 ± 0,4 (10)[a]
Risp 0,2 + Ket	32,2 ± 6,4 (10)[a]	2,6 ± 0,2 (10)[a]
Risp 0,2 + Ket	32,2 ± 6,4 (10)[a]	2,6 ± 0,2 (10)[a]

Values are reported as means ± e.p.m. for the number of mice shown in parentheses. a, b and c ($p<0.05$) as compared to control, Ketamine (Ket 10), and Hal 0.1, respectively. Analysis of variance and Tukey as the post-hoc test.

Discussion

Pharmacological experiments have demonstrated that subanesthetic doses of ketamine induce schizophrenia-like symptoms in humans [18] as well as behavioral activation in experimental animals [26]. The exact mechanism of this functional activation remains unknown. Duncan et al [27] suggested that relatively low doses of this drug produce several excitatory effects after systemic administration, and that these effects might result either from disinhibitory actions (e.g.: reduced activity of inhibitory neurons), or from disruption of the negative feedback regulation of excitatory amino acid-secreting neurons. This hypothesis can explain some studies which have revealed a lower density of glutamatergic receptors in brains of schizophrenic patients [28, 29]. In accord with this, latter finding [30] showed decreased glutamate binding in frontal cortex of subchronically ketamine-treated rats and suggested the use of this animal model for the study of this disease.

Similar to Yamamoto et al. [31], in this paper, we demonstrated that ketamine, acutely administered at low doses in mice, induces hyperactivity. It is well known that dopaminergic mechanisms play important role in the mediation of the locomotor activity, and ketamine may influence dopamine transmission and receptor activation via multiple mechanisms [32]. It is important to stress that biochemical data have shown that ketamine enhances dopamine release [33] and inhibits the dopamine [34] uptake in the striatum and

cortex, respectively. It has been suggested that ketamine may present an indirect dopamine agonist activity, and ketamine-induced behavioral stimulation may be connected with the dopamine system [35].

Conversely, Kapur & Seeman [36] suggested that ketamine might not be selective to NMDA receptors, but possesses high-affinity for dopamine and serotonin (5-HT_2) sites, acting as partial agonists at the D_2 receptors. However, different resuts were found by others authors. Liu et al. [26] reported that direct occupancy of dopamine D_2 and serotonin 5-HT_2 receptors by ketamine remains unclear, being necessary further investigation.

Regarding to neuroleptics, a decrease on locomotor activity showed an acute depressant effect of this class of drugs (Table 1). Among the pretreated groups, Risp 0.1 mg + Ket showed the most satisfactory results, reversing the locomotor hyperactivity to similar levels of the control group. The hypomotility caused by neuroleptics may result from a reduced excitability of the central nervous system or sedation [37]. Many antipsychotic drugs, including agents of low potency, present prominent sedative effects. This is particularly conspicuous early in treatment, although some typical tolerance can be developed [21].

Risperidone, an antipsychotic drug that presents antagonist properties on dopamine D_2, serotonin $5HT_2$ and α_1 adrenoreceptors, has been the focus of several clinical studies [38, 39]. The study carried out by Su et al. [40], using MK-801 (ketamine-like NMDA antagonist), showed that risperidone had an inhibitory effect on MK-801-induced hyperactivity in mice, at doses in which it caused no alteration in spontaneous activity when administered alone. This study also suggested that the inhibitory effect was mostly caused by the blockage of serotonin 5-HT_2A receptors and secondarily by the attenuation of dopamine D_2 and α_1 adrenoreceptors.

In respect to rearing and grooming (Table 1), the animals treated with ketamine and neuroleptics, except for haloperidol 0.1 mg (grooming), showed decreased responses in comparison to controls. This effect is possibly explained by the ataxia showed in the groups treated with ketamine. In mice pretreated with neuroleptics, the depressant effect seen in the locomotor activity test could have been possibly caused by sedation. Curiously, in Hal 0.1 mg group, the number of grooming did not differ from control.

Ketamine presents several neuropharmacological actions; however, the ability to block NMDA receptors most likely accounts for its psychotomimetic effects [41]. Such characteristic behavioral response consists on staggered locomotion and repetitive side-to-side head rocking [27, 42]. Similar results were obtained in our experiments after injection of Ket 10 mg; behavioral changes, including stereotyped behaviors, ataxia, and walking in circles (Figures 1 and 2) were present. Stereotyped activity in the Ket 10 mg group was significantly evident when compared to controls. The ataxia effect and stereotyped behavior were reversed by two classes of neuroleptics, however, risperidone did not reverse the walking in circles behavior. In accordance with these findings, studies in humans had demonstrated in never-medicated subjects with schizophrenia motor deficits resembling those of patients with primary striatum dysfunction, suggesting an involvement of these signs in the schizophrenic process [43, 44].

Results from the RR test showed that animals which received ketamine presented a decrease in the time of permanence on the bar and an increase in the number of falls

(Table 2), possibly due to the lack of motor coordination presented by this group. Haloperidol at the higher dose and risperidone at the lower dose increased the time of animal permanence in the bar, reflecting improvement in the motor coordination, however not sufficient to reduce the ketamine-increased number of falls. These data led us to suggest that such effect could be the result of an acute blockade of dopamine D_2 receptors in the striatum [45, 46]. The time of permanence on the bar of the groups treated exclusively with neuroleptics was not different from the controls, suggesting that the sedative effect of these drugs could contribute to the increased number of falls particularly at the higher doses, thus not being able to reverse the ketamine-increased number of falls in this test.

In the tail suspension, a test used to analyze antidepressant activity of drugs in animals, the ketamine-treated group presented a reduced immobility time, revealing an antidepressant effect (Figure 3). The reduced immobility was reversed by neuroleptics in all doses. The classic theory to explain depression is the monoaminergic hypothesis. It postulates that depression is related to a deficit of monoamines, especially serotonin and norepinephrine. However, other neuronal systems seem to be involved in the neurobiology and neurochemistry of the depression. One postulated hypotheses is the hypofunction of the dopaminergic system in depressant patients [47]. This idea is corroborated by the fact that chronic stress reduces basal release of dopamine; in addition, drugs with antidepressant action facilitate the dopaminergic transmission [48]. These results agree with behavioral studies suggesting that behavioral effects of NMDA antagonists are blocked by antipsychotic drugs [49, 50]. The action of these drugs in this model made possible the blockade of the symptoms caused by acute administration of ketamine.

In summary, the results obtained in this work showed that neuroleptics, under the mentioned experimental conditions, attenuated the increase of locomotor activity and stereotyped behavior, reversed the motor incoordination and blocked the hypermobility induced by acute administration of ketamine. The present results suggest that the ketamine mechanism of action may involve the dopaminergic system.

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Authors' Statements

Competing Interests

The authors declare no conflict of interest.

Animal Rights

The institutional and (inter)national guide for the care and use of laboratory animals was followed. See the experimental part for details.

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