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The metabotropic glutamate 2/3 receptor agonist LY379268 counteracted ketamine-and apomorphine-induced performance deficits in the object recognition task, but not object location task, in rats

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ABSTRACT

Experimental evidence indicates that the non competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine and the mixed dopamine (DA) D_1/D_2 receptor agonist apomorphine induce schizophrenia-like symptoms in rodents, including cognitive deficits. Activation of Group II metabotropic glutamate 2/3 (mGlu2/3) receptors reduces the excessive glutamate release that is hypothesized to be associated with psychiatric disorders. Thus, mGlu2/3 receptor agonists may reverse deficits induced by excessive glutamate or DA release induced by administration of NMDA receptor antagonists and DA receptor agonists, respectively, and potentially those seen in schizophrenia. LY379268 is a selective mGlu2/3 receptor agonist that has shown to be effective in several animal models of stroke, epilepsy, and drug abuse. The present study investigated whether LY379268 antagonizes non-spatial and spatial recognition memory deficits induced by ketamine and apomorphine administration in rats. To assess the effects of the compounds on non-spatial and spatial recognition memory, the object recognition task and object location task were used. Post-training administration of LY379268 (1–3 mg/kg, i.p.) counteracted ketamine (3 mg/kg, i.p.) and apomorphine (1 mg/kg, i.p.)-induced performance deficits in the object recognition task. In contrast, LY379268 (1–3 mg/kg, i.p.) did not attenuate spatial recognition memory deficits produced by ketamine (3 mg/kg, i.p.) or apomorphine (1 mg/kg, i.p.) in the object location task. The present data show that the mGlu2/3 receptor agonist LY379268 reversed non-spatial, but not spatial, recognition memory deficits induced by NMDA receptor blockade or DA receptor agonism in rodents. Thus, such mGlu2/3 receptor agonists may be efficacious in reversing some memory deficits seen in schizophrenia patients.

1. Introduction

Schizophrenia is a serious mental disorder that affects up to 1% of the population worldwide. Cognitive deficits in schizophrenia patients are core features of the illness and predict patients' vocational and social disabilities (Freedman, 2003). Numerous studies have indicated that the function of the glutamatergic system, particular *N*-methyl-D-aspartate (NMDA) receptors, might be compromised in schizophrenia. Exposure to non-competitive NMDA receptor antagonists like phencyclidine (PCP), MK-801, or ketamine induces behavioral symptoms in healthy individuals that resemble both the positive and negative symptoms of schizophrenia (Javitt and Zukin, 1991; Krystal et al., 1994) and exacerbate symptoms in schizophrenia patients (Lahti et al., 2001; Malhotra et al., 1997). Additionally, ketamine, PCP and MK-801 induce schizophrenia-like symptoms, including cognitive deficits, in rodents (de Lima et al., 2011; Pitsikas et al., 2008; Tricklebank et al., 1989; Verma and Moghaddam, 1996).

Dysfunction in dopaminergic (DAergic) neurotransmission has also been postulated in schizophrenia. Deficits in performance in

Abbreviations: AKT/GSK-3, glycogen synthase kinase-3; ANOVA, analysis of variance; CNS, central nervous system; D, discrimination; DA, dopamine; DAergic, dopaminergic; F, familiar; FL, familiar location; ITI, intertrial interval; i.p., intraperitoneally; LTP, long-term potentiation; mGlu, metabotropic glutamate; N, new object; NL, new location; NMDA, *N*-methyl-D-aspartate; PCP, phencyclidine; PRC, perirhinal cortex; PFC, prefrontal cortex; T1, sample trial; T2, choice trial.

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various cognitive tasks have been described in this disorder, linked to decreased prefrontal dopamine (DA) functioning (Iversen and Iversen, 2007). Evidence from both animal and human studies that pharmacologically stimulated DA receptors suggests that both too little and too much DA stimulation impairs cognitive performance (Cools, 2008; Gibbs and D'Esposito, 2005; Vijayraghavan et al., 2007; Gourgiotis et al., 2012).

Glutamate is the primary excitatory neurotransmitter in the mammalian central nervous system (CNS), acting on both ionotropic and metabotropic glutamate (mGlu) receptors. The mGlu receptor family consists of eight receptor subtypes that are divided into three groups based on sequence homology, pharmacological profile, and signal transduction pathways (Conn and Pin, 1997). Experimental evidence suggests that ligands for specific mGlu receptor subtypes have potential for the treatment of several CNS disorders, including depression, anxiety, schizophrenia, chronic pain, and epilepsy (Marek, 2004; Schoepp and Marek, 2002).

Group II mGlu receptors include mGlu2 and mGlu3 receptors. These receptors are localized primarily presynaptically in the cortex, thalamus, striatum, amygdala, and hippocampus, which are brain areas implicated in schizophrenia (Ohishi et al., 1993a, b; Petralia et al., 1996; Shigemoto et al., 1997). The activation of mGlu2/3 receptors provides a negative feedback mechanism to prevent excessive presynaptic glutamate release in limbic regions implicated in the pathophysiology of affective disorders (Chavez-Noriega et al., 2002; Schoepp and Marek, 2002). In this context, a previous study showed that the mGlu2/3 receptor agonist LY354740 reduced excessive glutamate levels and antagonized psychotomimetic effects and working memory deficits produced by the NMDA receptor antagonist PCP in rats (Moghaddam and Adams, 1998).

LY379268 is a selective agonist of Group II mGlu2/3 receptors, with higher affinity for these receptors compared with LY354740 (Monn et al., 1999). LY379268 has been reported to counteract hypermotility induced by PCP, ketamine (Cartmell et al., 1999; Lorrain et al., 2003b; Imre et al., 2006; Woolley et al., 2008), and amphetamine (Cartmell et al., 1999; Galici et al., 2005; Woolley et al., 2008), prevent PCP- and ketamine-evoked glutamate release in the hippocampus (Lorrain et al., 2003a), and increase DA levels in the prefrontal cortex (PFC) in rodents (Cartmell et al., 2000).

Presently, however, there is little evidence of the precise role of LY379268 in cognitive disorders related to schizophrenia. Evidence of the role of LY379268 in attentional deficits produced by either PCP or a neurodevelopmental manipulation intended to mimic the neuropathology of psychosis is quite conflicting. Specifically, treatment with this mGlu2/3 receptor agonist did not antagonize post-weaning social isolation-induced attentional deficits (Jones et al., 2011), and exacerbated the PCP-induced disruption of attentional performance in the five-choice serial reaction time test (5-CSRTT) in rats (Amitaij and Markou, 2010). By contrast, LY379268 has been shown to effectively counteract PCP-induced performance impairments in the 5-CSRTT in mice (Greco et al., 2005). With regard to learning and memory deficits related to schizophrenia, in procedures assessing acquisition of information (pre-test compound administration) this mGlu2/3 receptor agonist attenuated non-spatial recognition memory deficits induced by post-weaning social isolation (Jones et al., 2011), or by administration of MK-801 (Wieronska et al., 2013), and potentiated the ability of atypical antipsychotics (clozapine and lurasidone) to counteract non-spatial recognition memory deficits induced by PCP (Horiguchi et al., 2011) in rats. In addition, pre-training administration of LY379268 attenuated social memory impairments elicited by MK-801 in rats (Hikichi et al., 2013). However, it is not clear whether, in a procedure assessing the effects of compounds on storage and/or retrieval (post-training compound administration), LY379268 can reduce either non-spatial or spatial recognition memory impairments produced by dysfunction of the DAergic or glutamatergic system. The present study aimed to assess this issue.

Recognition memory stems from a series of neural processes by which a subject becomes aware that a stimulus has been previously experienced, with recognition as the behavioral outcome of these processes. This type of memory requires that the perceived characteristics of the events are discriminated, identified, and compared with the memory of the characteristics of previously experienced events (Steckler et al., 1998). Importantly, recognition memory is a type of memory that is impaired in schizophrenia patients (Calev et al., 1983; Edwards et al., 2002) and disrupted by both ketamine and apomorphine in young healthy volunteers (Morgan et al., 2004; Montoya et al., 2008) and rats (Boultadakis and Pitsikas, 2010; Gourgiotis et al., 2012).

Considering the aforementioned evidences, the aim of the present study was to evaluate the efficacy of LY379268 in counteracting ketamine and apomorphine-induced recognition memory deficits in rats. For these studies, the object recognition task (Ennaceur and Delacour, 1988) and object location task (Ennaceur et al., 1997) were used. These behavioral procedures assess non-spatial and spatial recognition memory, respectively, in rodents.

2. Material and methods

2.1. Animals

Independent groups of naive male 3-month-old Wistar rats (Hellenic Pasteur Institute, Athens, Greece), weighing 250–300 g, were used in each of the described experiments. The animals were housed in Makrolon cages (47.5 cm length × 20.5 cm height × 27 cm width), three per cage, in a climate-regulated environment (21 ± 1 °C; 50–55% relative humidity) under a 12 h/12 h (lights on at 7:00 AM) light/dark cycle with free access to food and water.

The procedures that involved animals and their care were conducted in conformity with international guidelines and national and international laws and policies (EEC Council Directive 86/609, JL 358, 1, December 12, 1987; *Guide for Care and Use of Laboratory Animals*, NIH publication no. 85-23, 1985).

2.2. Object recognition task

The test apparatus consisted of a dark open box made of Plexiglas (80 cm length × 50 cm height × 60 cm width) that was illuminated by a 60-W light suspended 60 cm above the box. The light intensity was equal in the different parts of the apparatus. The objects to be discriminated (in triplicate) were made of glass, plastic, or metal, and had three different shapes: (i.e., metallic cubes, glass pyramids, and plastic cylinders, 7 cm high) and could not be moved by the rats.

The object recognition test was performed as described previously (Boultadakis and Pitsikas, 2010; Ennaceur and Delacour, 1988). Briefly, during the week before the test, the animals were handled twice per day for 3 consecutive days. Before testing, the rats were allowed to explore the apparatus for 2 min for 3 consecutive days. During testing, a session that consisted of two 2-min trials was conducted. During the "sample" trial (T1), two identical samples (objects) were placed in two opposite corners of the apparatus in a random fashion, 10 cm from the side walls. A rat was placed in the middle of the apparatus and allowed to explore the two identical objects. After T1, the rat was returned to its home cage, and an intertrial interval (ITI) followed. Subsequently, the "choice" trial (T2) was performed. During T2, a novel object replaced one of the objects that was presented during T1. Accordingly, the rats were reexposed to two objects: a copy of the familiar (F) object and the novel (N) object. All combinations and locations of the objects were counterbalanced to reduce potential bias caused by preference for particular locations or objects. To avoid the presence of olfactory cues, the apparatus and objects were thoroughly cleaned with 20% ethanol after each trial and then wiped with dry paper.

Exploration was defined as the followings: directing the nose towards the object at a distance of 2 cm or less and/or touching the object with the nose. Turning around or sitting on the object was not considered exploratory behavior. The time spent by the rats exploring each object during T1 and T2 was manually recorded with a stopwatch. Based on this measure, a series of variables was then calculated: the total time spent exploring the two identical objects in T1 and the time spent exploring the two different objects, F and N in T2. The discrimination between the F and N objects during T2 was measured by comparing the time spent exploring the familiar object with the time spent exploring the novel object. Because this time may be biased by differences in the overall level of exploration (Cavoy and Delacour, 1993), we used a discrimination index (D) to represent the preference for novel objects as opposed to familiar objects, calculated as $D = (N - F/N + F)$ (Cavoy and

Delacour, 1993). We also evaluated locomotor activity measured as the total number of steps made by rats during T2 and the total time (in seconds) exploring the two objects (N and F) during T2.

2.3. Object location task

The test apparatus was the same apparatus as the one used in the object recognition task. The test arena was located in a large observation room with external cues (large and distinctive objects) that surrounded the experimental box to help rats complete the spatial memory task. These cues were kept in a constant location throughout the testing period. The objects were the same objects as in the object recognition task.

The object location task was performed as described elsewhere (Ennaceur et al., 1997; Pitsikas, 2007). Briefly, during the week before the test, the animals were handled twice daily for 3 consecutive days. Before testing, the rats were allowed to explore the apparatus for 2 min for 3 consecutive days. During testing, a session that consisted of two 2-min trials was conducted. During the "sample" trial (T1), two identical samples (objects) were placed in two opposite corners of the apparatus in a random fashion, 10 cm form the side wall. A rat was placed in the middle of the apparatus and allowed to explore these two identical objects. After T1, the rat was returned to its home cage, and an intertrial interval (ITI) followed. Subsequently, the "choice" trial (T2) was performed. During T2, one of the two similar objects was moved to a different location (new location [NL]) while the other object remained in the same position (familiar location [FL]) as in T1. Thus, the two objects were now in diagonal corners.

All combinations and locations of the objects were counterbalanced to reduce potential bias caused by preferences for particular locations. To avoid the presence of olfactory cues, the apparatus and objects were thoroughly cleaned as described above for the object recognition task.

The definition of exploration is provided above in the context of describing the object recognition protocol. The time spent by the rats exploring each object during T1 and T2 was manually recorded with a stopwatch. Based on this measure, a series of variables was then calculated: the total time spent exploring the two identical objects in T1 and the time spent exploring the two objects in the two different locations in T2. The discrimination between the FL and NL during T2 was measured by comparing the time spent in exploring the object in the FL with the time spent exploring the object in the NL. Because this time may be biased by differences in the overall level of exploration (Cavoy and Delacour, 1993), we used a discrimination index (D) to represent the preference for novel, as opposed to familiar object, location that was calculated as D = NL − FL/NL + FL (Cavoy and Delacour, 1993). We also evaluated locomotor activity measured as the total number of steps made by rats during T2 and the total time (in seconds) exploring the two objects (N and F) during T2.

2.4. Drugs

All of the drug solutions were freshly prepared on the day of testing and administered intraperitoneally (i.p.) in a volume of 1 ml/kg.

LY379268 ([-]-2-oxa-4-aminobicyclo[3.1.0.]hexane-4,6-di-carboxylic acid) was custom-synthesized and purchased from ANAWA (Wangen, Switzerland). LY379268 was dissolved in saline (0.9%, NaCl). To improve the solubility of the compound, 1 μl of 5 M sodium hydroxide (NaOH) per milligram of LY379268 was added to the solution (Jones et al., 2011). The solution was sonicated for 5 min, and the pH was adjusted to 7.4 using 1 M NaOH. The LY379268 doses (1 and 3 mg/kg) were selected based on the results of previous studies (Horiguchi et al., 2011; Jones et al., 2011).

Ketamine hydrochloride (Sigma, St. Louis, MO, USA) and apomorphine hydrochloride (Sigma, St. Louis, MO, USA) were dissolved in saline or saline that contained 0.1% ascorbic acid to prevent oxidation, respectively. The doses of ketamine (3 mg/kg) and apomorphine (1 mg/kg) were selected based on previous studies that indicated that these doses impaired recognition memory in rats without producing side effects (Pitsikas et al., 2008; Gourgiotis et al., 2012). In all of the experiments, control animals received isovolumetric amounts of the specific vehicle solution used in each study.

2.5. Experimental protocol

The experiments were conducted between 9:00 AM and 3:00 PM in a room where only these animals were housed. The animals' behavior was video-recorded. Data evaluation was subsequently performed by experimenters who were unaware of the pharmacological treatment of each subject.

2.5.1. Experiment 1: effects of LY379268 on ketamine-induced performance deficits in the object recognition task

The rats were randomly divided into six experimental groups (10 rats per group): vehicle + vehicle, 1 mg/kg LY379268 + vehicle, 3 mg/kg LY379268 + vehicle, 3 mg/kg ketamine + vehicle, 3 mg/kg ketamine + 1 mg/kg LY379268, and 3 mg/kg ketamine + 3 mg/kg LY379268. To examine the effects of the compounds on post-training memory components (storage and/or retrieval), the drugs were administered immediately after T1. For this study, the 1-h ITI was selected because non-spatial recognition memory is still intact in vehicle-treated rats with this delay condition (Bartolini et al., 1996), whereas impairments associated with ketamine (e.g., hypermotility, stereotypies, ataxia; Verma and Moghaddam, 1996) were not observed at this time point (Pitsikas et al., 2008).

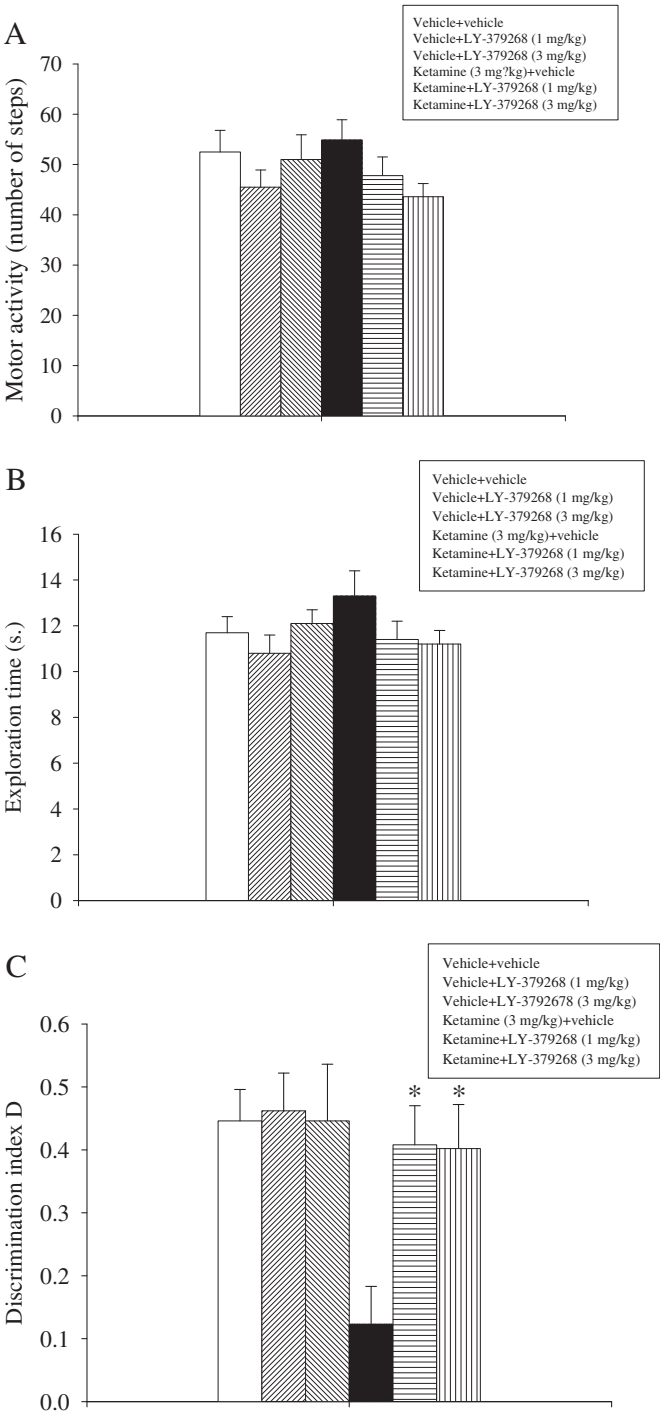

Fig. 1. Object recognition task. Vehicle, ketamine and LY379268 were injected intraperitoneally in rats immediately after T1. The results are expressed as mean ± SEM. (A) Total locomotor activity in the different groups during T2. (B) Total exploration time in the different groups during T2. (C) Discrimination (D) index in the different groups during T2. $^{*}p < 0.05$, compared with the ketamine plus vehicle-treated group.

2.5.2. Experiment 2: effects of LY379268 on apomorphine-induced performance deficits in the object recognition task

The rats were randomly divided into six experimental groups (10 rats per group): vehicle + vehicle, 1 mg/kg LY379268 + vehicle, 3 mg/kg LY379268 + vehicle, 1 mg/kg apomorphine + vehicle, 1 mg/kg apomorphine + 1 mg/kg LY379268, and

1 mg/kg apomorphine + 3 mg/kg LY379268. To examine the effects of the compounds on post-training memory components (storage and/or retrieval), the drugs were administered immediately after T1. Apomorphine (1 mg/kg) has been reported to induce hypermotility (Diaz et al., 1997) and produce a sustained increase in stereotypy (Moller et al., 1987) in rats, which return to baseline 1 h later (Diaz et al., 1997; Moller et al., 1987). In the present study, the 3-h ITI was selected because non-spatial recognition memory is still intact with this delay condition in vehicle-treated rats (Bartolini et al., 1996), whereas impairments associated with apomorphine administration were not observed at this time point (Gourgiotis et al., 2012).

2.5.3. Experiment 3: effects of LY379268 on ketamine-induced performance deficits in the object location task

The rats were randomly divided into six experimental groups (10 rats per group): vehicle + vehicle, 1 mg/kg LY379268 + vehicle, 3 mg/kg LY379268 + vehicle, 3 mg/kg ketamine + vehicle, 3 mg/kg ketamine + 1 mg/kg LY379268, and 3 mg/kg ketamine + 3 mg/kg LY379268. To examine the effects of the compounds on post-training memory components (storage and/or retrieval), the drugs were administered immediately after T1. In the present study, the 30-min ITI was selected because spatial recognition memory is still intact with this delay condition in vehicle-treated rats (our unpublished observations), and impairments associated with ketamine (e.g., hypermotility, stereotypies, ataxia; Verma and Moghaddam, 1996) were not observed at this time point (Pitsikas et al., 2008).

2.5.4. Experiment 4: effects of LY379268 on apomorphine-induced performance deficits in the object location task

The rats were randomly divided into six experimental groups (10 rats per group): vehicle + vehicle, 1 mg/kg LY379268 + vehicle, 3 mg/kg LY379268 + vehicle, 1 mg/kg apomorphine + vehicle, 1 mg/kg apomorphine + 1 mg/kg LY379268, and 1 mg/kg apomorphine + 3 mg/kg LY379268. To examine the effects of the compounds on post-training memory components (storage and/or retrieval), the drugs were administered immediately after T1. Apomorphine (1 mg/kg) has been reported to induce hypermotility (Diaz et al., 1997) and produce a sustained increase in stereotypy (Moller et al., 1987) in rats, which return to baseline 1 h later (Diaz et al., 1997; Moller et al., 1987). In the present study, the 2-h ITI was selected because non-spatial recognition memory is still intact with this delay condition in vehicle-treated rats (Bartolini et al., 1996), whereas impairments associated with apomorphine administration were not observed at this time point (Gourgiotis et al., 2012).

2.6. Statistical analysis

All of the data are expressed as mean ± S.E.M. The data were analyzed using the two-way analysis of variance (ANOVA). *Post hoc* comparisons between treatment means were made using Tukey's test. Values of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Experiment 1: effects of LY379268 on ketamine-induced performance deficits in the object recognition task

The overall analysis of the motility results and total object exploration time data during T2 did not show any effects of ketamine, LY379268, or their combination, reflected by an absence of statistically significant main and interaction effects (Fig. 1A and B, respectively). The analysis of the D index data revealed a significant main effect of ketamine ($F_{1, 59} = 6.738$, $p < 0.01$) a significant main effect of LY379268 ($F_{2, 59} = 3.250$, $p = 0.05$) but not ketamine × LY379268 interaction. Preplanned comparisons showed that the vehicle + ketamine group had a lower D index compared with all the other experimental groups, including the ketamine +1 mg/kg LY379268 and ketamine +3 mg/kg LY379268 groups ($p < 0.05$; Fig. 1C).

3.2. Experiment 2: effects of LY379268 on apomorphine-induced performance deficits in the object recognition task

The overall analysis of the motility data indicated a significant main effect of apomorphine ($F_{1, 59} = 9.944$, $p < 0.01$) but no main effect of LY379268 and no apomorphine × LY379268 interaction. Preplanned comparisons showed that locomotor activity during T2 in the apomorphine + 1 mg/kg LY379268 group was lower than in the vehicle + 1 mg/kg LY379268 group ($p < 0.05$; Fig. 2A). Total object exploration times were not different among the various experimental groups (Fig. 2B). The D index results revealed a significant apomorphine × LY379268 interaction ($F_{2, 59} = 6.050$, $p < 0.01$), and main effects of apomorphine ($F_{1, 59} = 2.943$, $p < 0.01$) and LY379268 ($F_{2, 59} = 4.461$, $p < 0.05$). The *post hoc* analysis demonstrated that the vehicle + apomorphine group had poorer discrimination than all the other treatment groups including the apomorphine +1 mg/kg LY379268 and apomorphine +3 mg/kg LY379268 groups ($p < 0.05$; Fig. 2C).

3.3. Experiment 3: effects of LY379268 on ketamine-induced performance deficits in the object location task

The overall analysis of the motility results and total exploration time data during T2 did not show any effects of ketamine, or LY379268 or ketamine × LY379268 interaction (Fig. 3A and B, respectively). The analysis of the D index data showed a significant main effect of ketamine ($F_{1, 59} = 21.668$, $p < 0.01$) but not LY379268 and no ketamine × LY379268 interaction. Preplanned comparisons revealed that all of the animals treated with ketamine had a significantly lower D index compared with their respective control groups ($p < 0.05$; Fig. 3C).

3.4. Experiment 4: effects of LY379268 on apomorphine-induced performance deficits in the object location task

The overall analysis of the motility data indicated a significant main effect of apomorphine ($F_{1, 59} = 8.2$, $p < 0.01$) but no effect of LY379268 and no apomorphine x LY379268 interaction. The *post hoc* analyses of treatment means values indicated that locomotor activity during T2 in the apomorphine +1 mg/kg LY379268 and apomorphine + 3 mg/kg LY379268 groups was lower than in the vehicle + 1 mg/kg LY379268 and vehicle + 3 mg/kg LY379268 groups ($p < 0.05$; Fig. 4A). Total exploration times were not different among the various experimental groups (Fig. 4B). The analysis of the D index data showed a significant main effect of apomorphine ($F_{1, 59} = 57.8$, $p < 0.01$), but no main effect of LY379268 and no apomorphine × LY379268 interaction. Preplanned comparisons revealed that all animals treated with apomorphine had a significantly lower D index compared with their respective control groups ($p < 0.05$; Fig. 4C).

4. Discussion

The object recognition task evaluates non-spatial recognition memory in rodents. It is a non-rewarded paradigm that it is based on spontaneous exploratory behavior in rodents (Ennaceur and Delacour, 1988). The object location task is a version of the object recognition task that evaluates spatial recognition memory. This task assesses the ability of rodents to discriminate the novelty of the object locations but not the objects itself because the behavioral testing arena is already familiar to the animals (Ennaceur et al., 1997). Both of these recognition memory tasks do not involve explicit reward or punishment but rely on the natural curiosity of rodents and preference for novelty (Robbins, 1977), which do not appear to be influenced by reinforcement/response contingencies (Dere et al., 2007). These paradigms are quite similar to procedures used in humans and should have a significant level of construct and predictive validity (Ennaceur and Delacour, 1988). As in the present study, the retention trial was performed no longer than 3 h after the sample phase, for the object recognition task and at 30 min for the object location task; thus the procedures employed can be regarded as tests of short-term memory.

The present results are consistent with previous studies, in which post-training administration of either ketamine or apomorphine disrupted performance in the object recognition task

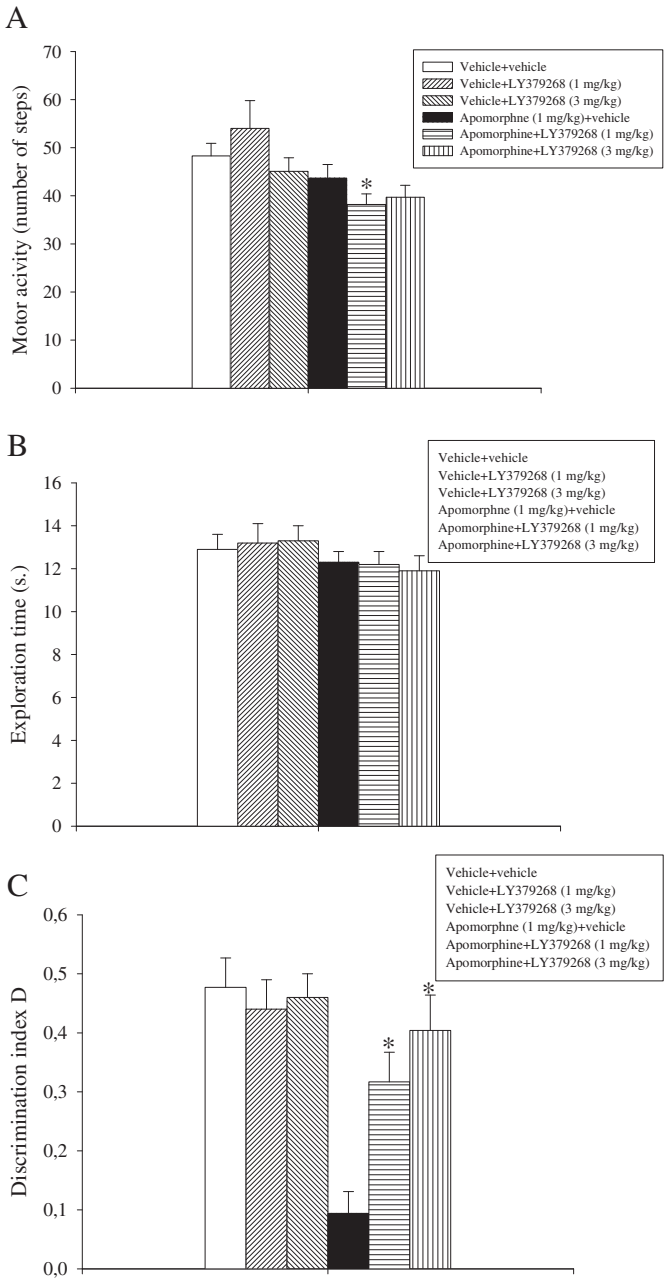

Fig. 2. Object recognition task. Vehicle, apomorphine and LY379268 were injected intraperitoneally in rats immediately after T1. The results are expressed as mean ± SEM. (A) Total locomotor activity in the different groups during T2. $^{*}p < 0.05$, compared with the respective control group. (B) Total exploration time in the different groups during T2. (C) Discrimination (D) index in the different groups during T2. . $^{*}p < 0.05$, compared with the apomorphine plus vehicle-treated group.

in rats (Boultadakis and Pitsikas, 2010; Gourgiotis et al., 2012), whereas ketamine disrupted performance in the object location task (Pitsikas et al., 2008). Treatment with LY379268 alone had no effect on recognition memory. A single post-training injection of LY379268 (1–3 mg/kg) attenuated both ketamine- and apomorphine-induced performance deficits in the object recognition task. The compounds (including LY379268) effects on performance during the retention phase reflect the modulation of post-training mnemonic processes (storage and/or retrieval of information). The present findings are consistent with previous reports in which LY379268 attenuated acquisition deficits revealed in non-spatial recognition memory procedures in a neurodevelopmental model of schizophrenia (Jones et al., 2011) or induced by NMDA in rats (Hikichi et al., 2013; Horiguchi et al., 2011; Wieronska et al., 2013). In addition, our results, for the first time to our knowledge, indicate that LY379268 reversed non-spatial recognition memory impairments related to DAergic dysfunction.

In contrast, LY379268 at all doses tested did not counteract the performance deficits produced by ketamine or apomorphine in the object location task. Several reasons might underlie this apparent discrepancy. The lack of a protective effect of LY379268 in the object location task may stem from the fact that spatial memory is more susceptible to hippocampal dysfunction than non-spatial memory

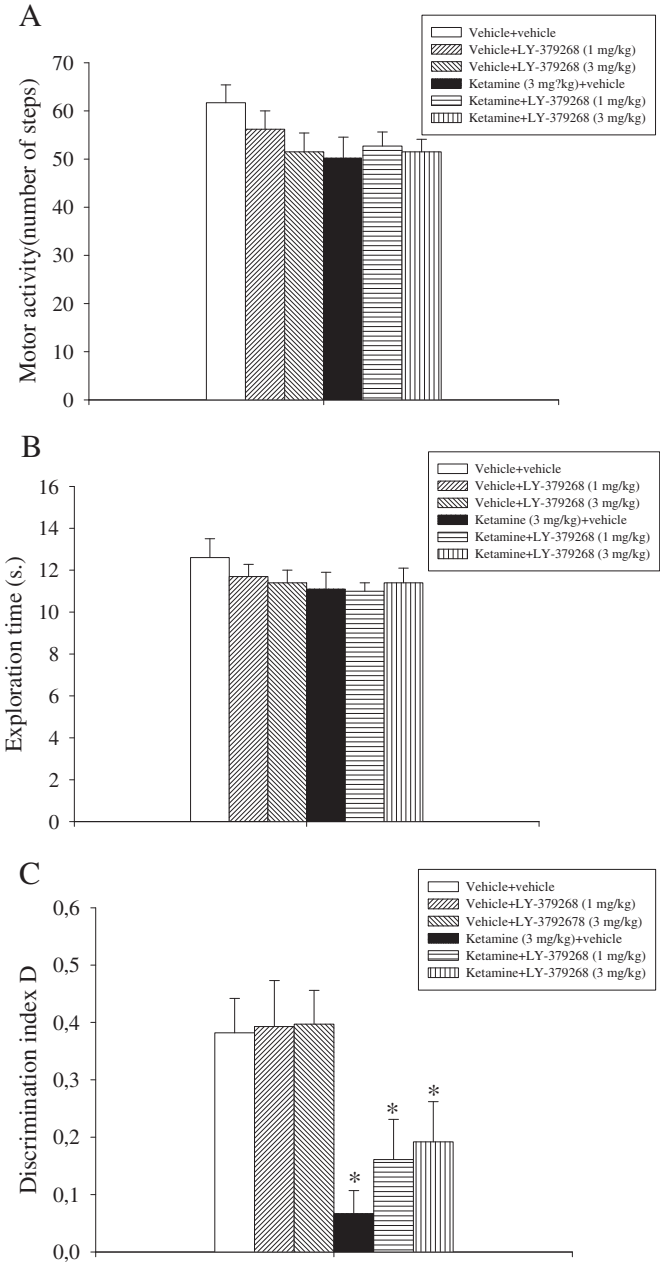

Fig. 3. Object location task. Vehicle, ketamine and LY379268 were injected intraperitoneally in rats immediately after T1. The results are expressed as mean ± SEM. (A) Total locomotor activity in the different groups during T2. (B) Total exploration time in the different groups during T2. (C) Discrimination (D) index in the different groups during T2. $^{*}p < 0.05$, compared with respective control groups.

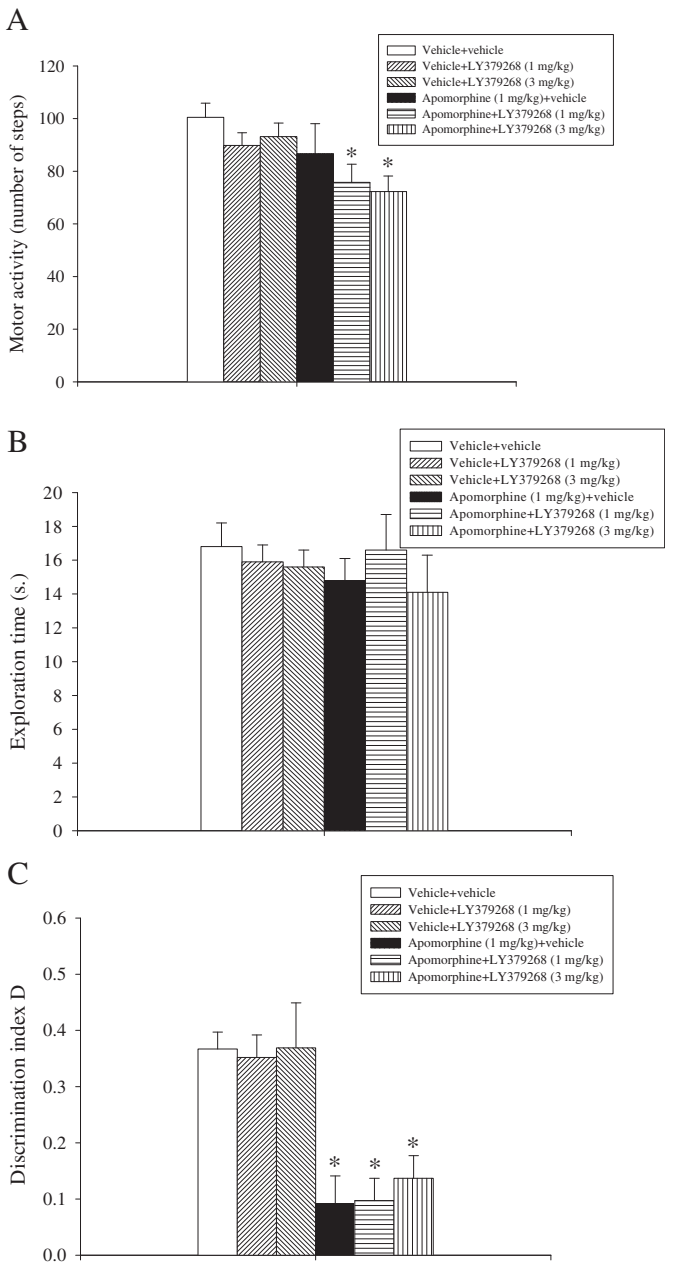

Fig. 4. Object location task. Vehicle, apomorphine and LY379268 were injected intraperitoneally in rats immediately after T1. The results are expressed as mean ± SEM. (A) Total locomotor activity in the different groups during T2. $^{*}p < 0.05$, compared with respective control group. (B) Total exploration time in the different groups during T2. (C) Discrimination (D) index in the different groups during T2. $^{*}p < 0.05$, compared with respective control groups.

(object recognition procedure). Lesions of at least 80% of the hippocampus are necessary to impair object recognition, whereas smaller lesions of the hippocampus (30%) impair spatial memory tasks. Thus, performance in the spatial object location task is easier to disrupt than performance in the non-spatial object recognition task, making performance in this task less susceptible to LY379268 administration (Broadbent et al., 2004). In this context, it has been reported that object location is more vulnerable than object recognition because it is based on a less redundant information: the various features of the objects can be encoded from several dimensions and attributes, which are not all required during recognition, while a location offers fewer cues (Ennaceur and Meliani, 1992; Ennaceur et al., 2005). Collectively, tests of spatial memory typically tax the ability of the animal to discriminate between two or more highly familiar locations, often on the basis of which the animal has last visited, set within a familiar environment while non-spatial tasks often involve stimuli that are relatively unfamiliar or completely novel. Thus, this difference in stimuli intensity (higher in non-spatial tasks as compared to spatial tasks) might underlie the longer preservation of memory in the object recognition with respect to the object location (Dix and Aggleton, 1999). In support of this view, we have observed, under our experimental conditions that non-spatial recognition memory persists up to 3 h (Boultadakis and Pitsikas, 2010; Gourgiotis et al., 2012; present results), while spatial recognition memory is extinguished after 1 h in control rats (Pitsikas, 2007). Finally, previous work examining the effects of LY379268 on memory deficits related to schizophrenia evidenced that this mGlu2/3 agonist was found efficacious in non-spatial memory tasks which did not require reinforcement (Hikichi et al., 2013; Horiguchi et al., 2011; Jones et al., 2011; Wieronska et al., 2013). Our results are consistent with the above findings.

Regarding the effects of mGlu2/3 receptor agonists on spatial memory, the role of these receptors appears controversial since either impairments in the normal rat were revealed or these compounds were unable to reverse memory deficits (for review, see Marek, 2010). Recently, however, it has been reported that LY379268 attenuated spatial memory deficits elicited by pre-retrieval treatment with MK-801 in rats (Blot et al., 2014). In spite of this finding, important differences underlie the results of this study with respect to the present findings. The delayed spatial alternation task used in the study by Blot and colleagues, is a food-rewarded procedure, whereas the object location task used in the present experiment is a non-reinforced spatial memory procedure. Moreover, in that study LY379268 counteracted long-term spatial memory deficits, but in line with the present results, LY379268 did not attenuate short-term spatial memory deficits. These considerations probably offer a plausible explanation as to why LY379268 did not reverse the ketamine and apomorphine-induced deficits in the object location task.

The compounds were administered systemically in the present study. Thus, non-specific factors such as attentional or sensorimotor deficits may have influenced performance. However, the influence of these factors on D index (a measure of recognition memory) is unlikely because the rats were tested at least 30 min after drug administration when the presumed effects of all of the drugs tested on these factors mostly wore-off. Additionally, no differences in either locomotor activity or general exploratory activity were observed during T2 among the different experimental groups, with the exception of the groups that received apomorphine or LY379268 only. Although the latter groups of rats displayed lower levels of motility, their total exploration time during T2 was not different from their vehicle-treated cohorts. The effects of ketamine and apomorphine on memory were also unlikely attributable to the residual presence of the drug during testing because these compounds have a very short half-life (10–15 min; Bianchi et al., 1986; Krystal et al., 1994). Therefore, this pattern of results suggests that the effects of the compounds on cognitive performance were unrelated to potential effects on motility and exploratory behavior.

The mechanism by which ketamine produces its psychotomimetic effects has been at least partially attributed to the blockade of NMDA receptors located on γ-aminobutyric acid (GABA) interneurons, which in turn leads to the disinhibition of neural activity in limbic structures (Moghaddam et al., 1997). This disinhibitory action increases neuronal activity and causes excessive glutamate and DA release in the PFC and limbic regions (Moghaddam et al., 1997; Razoux et al., 2007).

Alterations in the DA activity in the dorsolateral PFC haves been suggested to underlie the detrimental effect of apomorphine on cognition (Fletcher et al., 1996; Friston et al., 1992). However, apomorphine was administered systemically in the present study, and changes in DA neurotransmission in other brain areas, such as the striatum, cannot be discarded. The PFC and striatum are part of the cortico-striatal-thalamic loop (Alexander et al., 1990). Substantial evidence indicates that the manipulation of neural functions in the PFC and the striatum similarly affects cognitive, motor, and reward processes. Specifically, some nodes of corticostriatal circuitry, such as those involved in the prelimbic area of the PFC and ventral striatum (i.e., nucleus accumbens), have also been shown to play a role in the acquisition and storage of information that is essential for the coding of novel environmental information (Setlow, 1997) as those engaged by the object recognition memory (Sargolini et al., 2003). Functional studies have suggested that interactions between dopaminergic and glutamatergic inputs in the ventral striatum dictate the outcome of processing salient environmental information (Coccurello et al., 2012).

The mechanisms by which LY379268 exert its effects on ketamine-induced behavioral deficits are still under investigation. The schizophrenia-like effects of NMDA receptor antagonists include increased levels of glutamate, hypermotility, stereotypy, and cognitive deficits (Moghaddam et al., 1997; Moghaddam and Adams, 1998). Interestingly, LY379268, similarly to LY353740 (Moghaddam and Adams, 1998), reduced excessive glutamate and GABA levels (Cartmell and Schoepp, 2000; Lorrain et al., 2003a) and counteracted the psychotomimetic effects produced by ketamine (Lorrain et al., 2003b) and PCP (Cartmell et al., 1999). Collectively, these findings suggest that this reduction of glutamate and GABA levels by LY379268 might be critical for the beneficial effect of LY379268 on ketamine-induced non-spatial recognition memory deficits. In this context, it is important to emphasize that the reversal by LY379268 of cognitive deficits induced by NMDA blockade in the object recognition task might be dependent on the 5-HT_{1A} receptor (Wieronska et al., 2013).

An alternative hypothesis that may explain the present results is based on recent findings that provide evidence for postsynaptic mechanisms of mGlu2/3 receptors in the regulation of NMDA receptors. Specifically, LY379268 was shown to modulate the function of NMDA receptors through postsynaptic actions and reversed MK-801-induced NMDA dysfunction via the glycogen synthase kinase-3 (AKT/GSK-3) pathway (Xi et al., 2011).

The mechanism by which LY379268 exerts its effects on apomorphine-induced non-spatial recognition memory impairment is not yet clear. Additional studies are needed to address this issue. LY379268 was shown to reverse amphetamine-induced hyperactivity in rodents (Cartmell et al., 2000; Galici et al., 2005). Furthermore, LY379268 increased extracellular DA levels in the rat PFC (Cartmell et al., 2000). This latter finding is interesting because alterations in DA activity in the dorsolateral PFC haves been suggested to underlie the detrimental effect of apomorphine on cognition (Fletcher et al., 1996; Friston et al., 1992).

mGlu2 receptors are highly expressed in perirhinal cortex (Woolley et al., 2008). There is experimental evidence that perirhinal cortex is involved in human recognition memory (Yassa and Stark, 2008). Thus, the mGlu2/3 receptors in perirhinal cortex might contribute to the ability of atypical antipsychotics, such as clozapine to ameliorate the recognition memory deficits elicited by NMDA blockade (Horiguchi et al., 2011).

Previous work demonstrated that LY379268 did not antagonize PCP-induced hypermotility and attentional deficits in rodents (Henry et al., 2002). Furthermore, recent clinical research indicated that the mGlu2/3 receptor agonist pomaglumetad (LY2140023) did not improve symptoms in schizophrenia patients (Adams et al., 2013; Stauffer et al., 2013). Considering the above findings, the present results suggest a potential role for LY379268 as an adjunctive agent, for the treatment of some aspects of schizophrenia such as cognitive deficits.

5. Conclusions

In summary, the present results suggest that the mGlu2/3 receptor agonist LY379268 may counteract non-spatial but not spatial recognition memory deficits induced by abnormalities of the glutamatergic and DAergic system evidenced, for the first time to our knowledge, in a procedure assessing storage and/or retrieval of information. Thus, these present findings support a potential therapeutic role of mGlu2/3 receptor agonists in the treatment of some behaviors that may have translational relevance to human visual memory. Therefore, compounds with agonist or positively modulatory actions on mGlu2/3 receptors may effectively treat some of the memory deficits seen in schizophrenia patients.

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