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Social memory in mice: Disruption with an NMDA antagonist and attenuation with antipsychotic drugs

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ABSTRACT

Social recognition reflects the ability of one animal to learn and remember the identity of another. Animal models of social learning and memory are pertinent to several different CNS diseases involving disruptions in cognition. Moreover, the increased understanding of the basic biology of memory increases the likelihood of discovery of memory-enhancing treatments in these human diseases. In the present study, we investigated the effects of the non-competitive NMDA antagonist ketamine on social recognition in mice across a broad dose range (5–30 mg/kg) and time-course (60 min–7 days). We also tested the ability of two antipsychotic drugs, haloperidol and olanzapine, to block the ketamine effect. Our results show that mice demonstrate social recognition over a several day period, with loss of recognition between 3–7 days. Ketamine disrupts social memory at doses which do not affect task performance. Chronic oral administration of haloperidol or olanzapine attenuates these ketamine-induced effects on social recognition, tending to normalize the memory behavior. The neural mechanisms of these actions are not known, although medial temporal lobe memory systems have been implicated.

1. Introduction

Social memory is an important component of survival in animal groups, and is based on relational learning of complex stimuli in a social environment (Lai et al., 2005). Animals recognize each other on the basis of multimodal sensory characteristics, conjunctively encoded (Thor and Holloway, 1982; Bluthe and Dantzer, 1993; Dluzen and Kreutzberg, 1993). Under laboratory conditions, social learning and memory in animals can be studied by exposing rodents to each other for an initial meeting, then testing their recognition as a function of time. When two rodents are exposed to each other for a specified period of time, re-exposure of the two animals at a subsequent episode is characterized by a shorter investigation time. This foreshortened time is taken to represent the social recognition (Thor and Holloway, 1982; Bluthe and Dantzer, 1993; Dluzen and Kreutzberg, 1993). Social recognition in rodents and primates has been shown to be dependent on hippocampal function in that ablations of the hippocampus block social recognition (Kogan et al., 2000; Maaswinkel et al., 1996; Wimersma Greidanus and Maigret, 1996; Baker and Kim, 2002). Moreover, persistent social memory (longer than 24 h) is dependent on changes in cyclic AMP responsive element binding (CREB) and protein synthesis (Kogan et al., 2000; Richter et al., 2005). Several memory systems exist in brain partitioned by region; the prefrontal cortex is implicated in working memory, the medial temporal lobe (MTL), in declarative memory, and the basal ganglia, in procedural memory. The MTL brain regions implicated in declarative memory facilitate conscious memory for events and facts (Wagner et al., 1998; Davachi et al., 2003; Bayley et al., 2005). The MTL memory circuit encodes information about prior objects and events and reactivates this knowledge to inform present decisions and actions (Dluzen and Kreutzberg, 1993; Corkin, 1984; Squire et al., 2004). Hippocampal subfields play distinct roles in memory function as do regions along the MTL rostrocaudal axis (Small et al., 2001; Preston et al., 2005; Amaral and Witter, 1989). Clinical evidence implicates hippocampal dysfunction in several diseases of cognition, including Alzheimer's dementia (Zarow et al., 2005), depression (Campbell and Macqueen, 2004; Sala et al., 2004), post-traumatic stress disorder (PTSD) (Bremner and Vermetten, 2004) and schizophrenia (Medoff et al., submitted for publication); therefore, animal cognition, especially those behaviors requiring hippocampal mediation, could have broad disease relevance.

Phencyclidine (PCP) is often used in animals to model human psychosis (Jentsch and Roth, 1999), based on its known psychotomimetic properties in humans (Pearlson, 1981; Tamminga, 1999). NMDA-sensitive glutamate receptors are localized in high density within cortex and basal ganglia, where PCP provides a non-competitive blockade at the NMDA ionophore. In MTL, glutamate positively modulates what are thought to be some of the cellular processes underlying recognition, learning and memory through enhancement of long term potentiation (LTP) (Malenka and Nicoll,

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1999; Kandel, 2001). Among the many actions of PCP on brain chemistry are those we have previously reported, that include dynamic and potent neuronal activation (Gao et al., 1993), an extended alteration (biphasic in nature) in NMDA receptor density (Gao and Tamminga, 1995; Gao and Tamminga, 1994, 1996), and dynamic changes in immediate-early gene expression (Gao et al., 1998), all of which occur most dramatically in the hippocampus. These data suggest that PCP and its congeners, including ketamine, (Martin and Lodge, 1988) can directly disrupt cerebral neurochemistry and function in multiple brain regions including hippocampus.

Social cognition is an aspect of learning and memory that is particularly impaired in psychotic disorders, including schizophrenia and bipolar disorder (Kuperberg and Heckers, 2000; Nuechterlein et al., 2005). The possibility that this disturbance in human social cognition could be mimicked in animals using ketamine and measured using social memory was attractive, given the current focus on cognition in psychotic illnesses (Hyman and Fenton, 2003). We hypothesized that ketamine, by blocking the NMDA-sensitive glutamate receptor in brain, would impair social cognition in mice through glutamatergic mechanisms (Javitt and Zukin, 1991). Using the same line of reasoning, we anticipated that antipsychotic treatment might attenuate the ketamine action since they improve cognition from the untreated state in schizophrenia. Therefore, in these experiments, we sought to test the effects of NMDA blockade with ketamine on social learning in mice. We examined the effects of ketamine on social recognition behavior across a dose range and a time-course in mice. Then, we studied the effects of a first (haloperidol) and a second (olanzapine) generation antipsychotic drug on those ketamine-induced disruptions in social learning.

2. Materials and methods

2.1. Animals

Adult (8–12 weeks) and juvenile (4–5 weeks) male C57BL/6J mice were purchased from Jackson Laboratory (Bar Harbor, Maine). Animals were housed 4–5 per cage and given food and water ad libitum. Lighting followed a 12:12-h light–dark cycle and the experiments were always conducted during the light phase of the cycle. Juvenile mice were used as the stimulus animals to minimize aggression. New sets of animals were used for each experiment; no mouse was tested at more than one evaluation time or drug dose. The experimental protocol for these studies was approved by the Institutional Review Committee for the University of Maryland at Baltimore, covering the use of animal subjects, in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals.

2.2. Social memory assessment

To assess social memory in mice, we followed the method described by Thor and Holloway (Thor and Holloway, 1982). The test is based on the tendency of an adult mouse to investigate an unknown juvenile mouse. Overall, in this paradigm, two mice (one adult and one juvenile) are exposed to each other for a short time (2 min), and the time that the adult explores the juvenile is measured. Then, mice are re-exposed at fixed inter-trial intervals; at the second ('trial') exposure, the duration of their investigation is characteristically reduced. The decrement in investigation time between the first and second exposure is used as an indication of social memory. Animal testing in this experiment was not conducted during the normally active period, because constraints on the housing facility prohibited a reverse light–dark cycle. Our concern that the housing conditions would interfere with the behavioral assay was mitigated by the successful control conditions.

On the day of the first exposure, group housed adult and juvenile mice were brought to the observation room to acclimate to the environment. An adult mouse was then placed into a 29 cm×18 cm×12 cm empty plastic cage under dim light and allowed to habituate to the test environment for 15 min. Following the 15 min acclimation period, a juvenile mouse was placed into the cage with the adult mouse for 2 min. The duration of the social investigatory behavior within the two minute period was scored by a trained observer. The social investigatory behavior which was quantified included direct contact or sniffing, following, nosing, grooming, pawing or generally inspecting any body surface of the novel juvenile mouse within 1 cm (Thor and Holloway, 1982). The re-exposure at a fixed interval between the same adult and juvenile pair was conducted exactly like the first exposure. The interval between the first exposure and the test trial was 10, 30, 60, 120 min, 1 day, 3 days, 7 days, 15 days or 30 days. A minimum initial investigation time (we adopted 24 s from Kogan et al., 2000) was required to qualify for an exposure test. A new set of mice was used for assessing each intertribal interval and each new experiment.

2.3. Drug administration

2.3.1. Ketamine

Doses of ketamine (10–30 mg/kg, i.p.) were administered to mice 20 min prior to their initial social learning exposure. Each ketamine dose group had a saline control (N=10, each dose group). Ketamine was obtained from Fort Dodge Animal Health (Fort Dodge, Iowa) and diluted in sterile saline. The social recognition behavior was tested at 10–120 min and 1–30 days after 10 mg ketamine administration. Because ketamine causes a decrease in locomotion behavior at high doses (tested from 5–30 mg/kg, i.p., Table 1), we set 10 mg as the highest ketamine dose when administered *before* testing social learning. In another paradigm, to test the effect of ketamine on only the consolidation phase of learning, we administered ketamine to a set of mice, not previously exposed to the learning environment, immediately *after* their initial social exposure. Here, we tested doses of up to 30 mg/kg; there was no need to restrict doses because, for consolidation, the social learning was assessed 1–3 days after ketamine when any locomotor effects were gone.

2.3.2. Antipsychotic drug administration

Three groups of mice were treated with water alone, haloperidol in water (2 mg/kg/day) or olanzapine in water (4 mg/kg/day), respectively as the only solution available in their home cage water bottle. Drugs were dissolved in drinking water as previously described (Gao et al., 2005) and administered for 30 days prior to testing. The two test drugs, haloperidol and olanzapine, were separately dissolved in a minimum volume of glacial acetic acid. Each solution was diluted with distilled water and adjusted to PH 5.5 to 6.0, using 10 N NaOH. For the haloperidol solution, the stock was kept at 0.33 mg/ml, and diluted to 3.3 mg haloperidol in 100 ml solution within 7 days of administration. For the olanzapine solution, the stock was kept at 0.67 mg/ml, and diluted in 100 ml solution within 7 days of administration.

The dose of drug chosen for each compound was based upon extensive studies done in the rat (Gao et al., 1998). The drinking water concentrations of drug known to produce plasma drug concentrations

Table 1
Dose effects of ketamine on initial investigation time

Treatment	Dose (mg/kg)	Investigation time (s)	Qualifying mice (%)
Saline	0.1 ml/10 g	54.4±13.7	75
Ketamine	5	45.2±6.4	75
Ketamine	10	47.6±18.3	75
Ketamine	20	45.8±16.7	50
Ketamine	30	44.0±28.2	25

The investigation time is reported only for the qualifying mice, the percentage of which is noted in the last column. These data were used to identify the highest dose of ketamine that failed to decrease the percentage of investigation time compared with saline as 10 mg/kg.

Table 2
Plasma drug concentrations in C57BL/6J mice

Drug (mg/kg/day)	Drug plasma level (ng/ml) mean ± SD	Human therapeutic plasma range (ng/ml)
Haloperidol (2)	7.94 ± 2.1	4–16
Haloperidol (5)	12.5 ± 3.7	4–16
Olanzapine (4)	31.75 ± 16.1	10–30
Olanzapine (8)	37.5 ± 10.6	10–30

in rat within the human therapeutic range were known; we extrapolated the dosing from the rat to the mouse in order to obtain a similar plasma concentration of each drug in mouse. In order to verify that the concentration extrapolated from rats resulted in appropriate plasma levels in the mouse, we evaluated it. Twenty adult mice were given a 2 week treatment with haloperidol ($N=10$) or olanzapine ($N=10$), each at two doses, in their drinking water. Plasma was collected by cardiac puncture after 2 weeks and was frozen at −20 °C until analysis for drug levels. Plasma drug concentrations were determined using HPLC and mass spectroscopy in the laboratory of Thomas Cooper (Nathan Klein Institute). Plasma levels after 2 weeks at two dose levels of haloperidol and olanzapine are given in Table 2.

When evaluating social memory, each chronically treated animal group (haloperidol at 2 mg/kg/day, olanzapine at 4 mg/kg/day, and water alone) was evenly divided into two groups; one group was injected with saline and the other with ketamine (10 mg/kg) 20 min before social learning testing. The inter-trial interval for evaluation of the antipsychotic drug effect was 3 days. Mice were treated with the antipsychotic drug during the 3 day interval.

2.4. Data analysis

2.4.1. Statistical analysis

A two-factor repeated measures analysis using mixed linear models was used to test the interval and trial effect on social recognition with and without ketamine treatments (Figs. 1 and 2 respectively). In these models, the factors include the exposure interval (the between group factor), trial (the repeated factor, e.g., initial versus trial), and the interaction between interval and trial. A significant interaction indicates that there are different responses between the groups (exposure intervals or treatments) that are being compared. To test the ketamine effect (Figs. 2 and 3), a similar model, but with ketamine dose as the between group factor, was used. The antipsychotic drug effect and antipsychotic drug effect distributed by ketamine and trial effect under different treatments were assessed by a three factor repeated measures model (Fig. 4). The alpha = 0.05 level of significance was used to test for significant main effects and interactions from the models. Multiple comparisons were made via least squares means contrasts derived from these mixed linear models. For testing the significance of the trial effect in nine exposure interval groups (Fig. 1), the Bonferroni–Holm method was used to adjust for multiple testing. For other experiments, p-values were adjusted, using the Bonferroni–Holm approach, for comparisons between three trials, i.e., three trial intervals (Fig. 2),

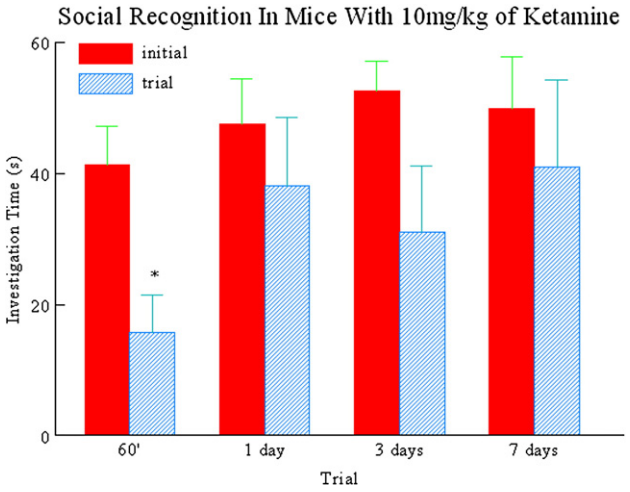

Fig. 2. Ketamine at a dose of 10 mg/kg (administered BEFORE the initial exposure) disrupted the recognition of a juvenile mouse by an adult animal at 1 and 3 day inter-trial intervals (long term), but not after a 60 minute interval (short term). Distinct animal pairs were used for each dose group.

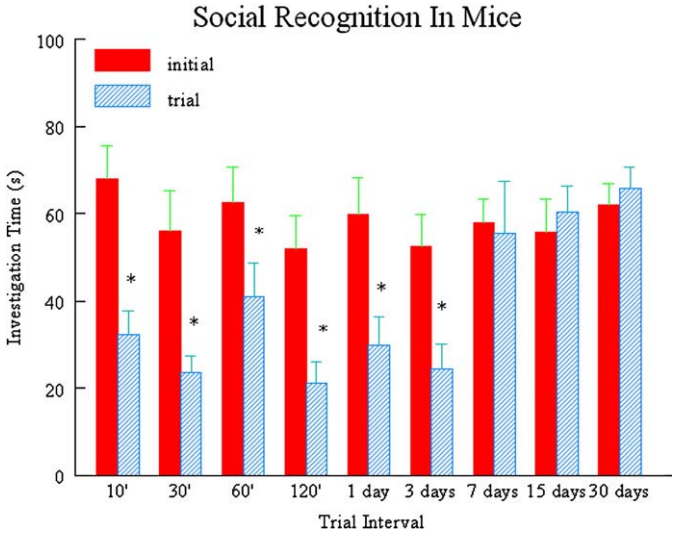

Fig. 1. The time in seconds that an adult mouse investigated a juvenile mouse at an initial meeting (filled bar) compared with a trial meeting (crossed hatched bar) at inter-trial intervals of 10 min to 30 days. New animal pairs were used for each time interval. There was a significant reduction in the exploration time at the trial meeting between the animals beginning at 10 min and lasting up to 3 days. This recognition behavior was lost by 7 days.

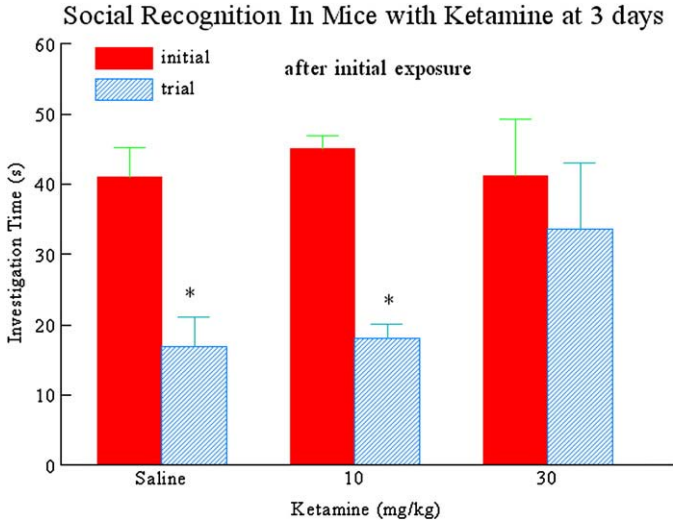

Fig. 3. Ketamine was administered at a dose of 10 mg/kg or 30 mg/kg (AFTER the initial exposure) and was evaluated at 3 days. Social recognition was disrupted with 30 mg/kg ketamine but not at 10 mg/kg, showing that ketamine could disrupt the consolidation of the social recognition memory but only at higher dose levels.

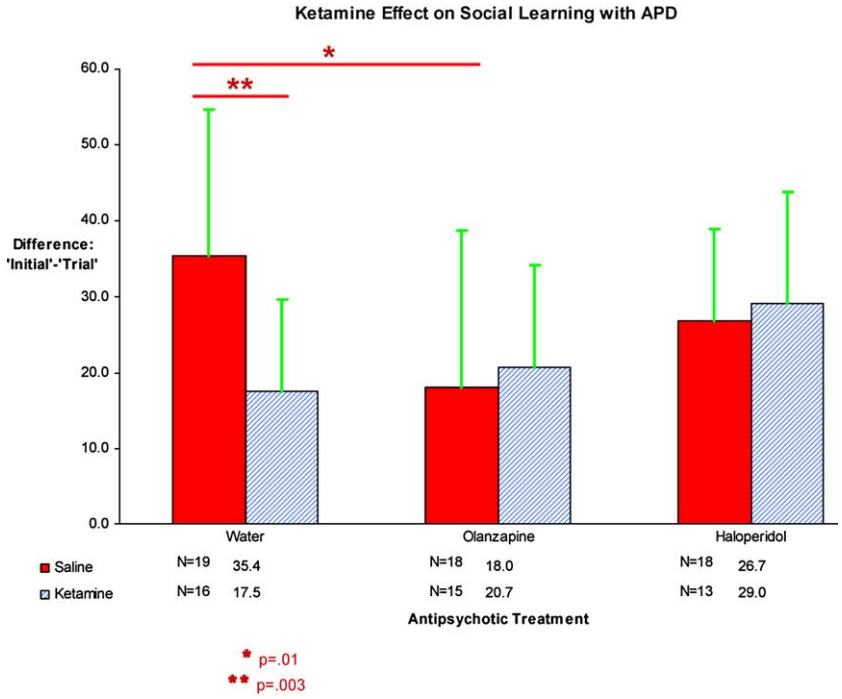

Fig. 4. Ketamine or saline was administered just before the "initial" exposure between two animals making up three different groups, those that were treated with water only, haloperidol (2 mg/kg/day) or olanzapine (4 mg/kg/day) for 30 days. At the "trial" exposure, social recognition was present in the water/saline condition but reduced by water/ketamine; while subchronic treatment with olanzapine but not haloperidol reduced the initial responding, both antipsychotic drugs (haloperidol/ketamine and olanzapine/ketamine) blocked the disruptive action of ketamine on social learning.

three doses (Fig. 3), or three treatments (Fig. 4). Statistical analysis was performed with SAS 9.1.3 (SAS Institute, Cary, NC).

3. Results

3.1. Social recognition behavior in mice

The recognition behavior of an adult mouse toward a previously explored juvenile mouse was assessed by measuring the investigation time during the re-exposure of the adult to the juvenile after varying inter-exposure intervals (Fig. 1). The results show that C57BL/6J adult mice show a significant reduction in the duration of investigation of a familiar juvenile mouse. This reduction was significant over inter-exposure intervals (ANOVA, Interval×Trial interaction, $F_{(8,\ 68)}=4.88$, $p<0.0001$). This change was observed immediately after an initial exposure (mean change 35.6 s, SD 19.1) and could still be detected at 3 days (mean change 32.9 s, SD 28.3). A significant decrease in duration was observed at each inter-trial interval between 10 min and 3 days, Bonferroni–Holm adjusted p-values of 0.03 to 0.0009. However, differences were not detected at or beyond 7 days, with these inter-trial intervals having smaller mean changes of 3.1, −4.6, and −3.8 s at 7,15, and 30 days, respectively, adjusted $p=1.0$ within each interval. The reduction in investigation time is taken as an indication of learning which transpires at the initial animal exposure. There was no difference in exploration behavior during the initial exposure across all groups, ANOVA $p=0.99$. In our hands, as in other laboratories, inhibition of protein synthesis with anisomycin blocked this social memory at inter-trial intervals beyond 24 h (data not shown).

3.2. Ketamine-induced disruption of social recognition

Prior to evaluating ketamine in the social recognition paradigm, the acute effect of increasing doses of ketamine on exploration times in the adult mouse was evaluated to rule out a nonspecific locomotor effect of the drug on exploration. The criterion for a valid initial test was adopted from Kogan et al. (2000), namely that the mice show at least 24 s of total exploration time during the 2 min exposure. The number of animals who failed to reach this criterion increased with increasing doses of ketamine (Table 1). Because a decrease in exploration time may confound the evaluation of social memory, we set 10 mg/kg of ketamine as the upper limit for testing the drug's ability to disrupt social recognition whenever the drug was administered before the evaluation of social recognition, when the first decrease in exploration time was noted. When ketamine was administered after the evaluation of social recognition (e.g., when it was used to evaluate disruption of memory consolidation), higher doses could be evaluated, because social learning was not tested until 1–3 days later. However, all data reported in this paper come only from mouse pairs who met the exploration criterion of 24 s exploration per 2 min test interval, regardless of ketamine dose.

Social recognition was evaluated in the adult mouse after ketamine over inter-trial intervals of 60 min, 1, and 3 days (Fig. 2). Social memory at 60 min was not impaired by ketamine, with a mean 25.5 s, SD=17.5 test-initial investigation time, $p=0.03$, indicating that ketamine, per se, does not interfere with memory acquisition. Whereas, social memory at more distant times appeared ketamine-sensitive, indicated by a loss of the reduction in exploration time at inter-trial intervals of 1 and 3 days (mean reduction 9.3, SD=16.3, $p=0.28$ and mean reduction 21.7, SD=30.1, $p=0.06$, respectively) (Fig. 2).

To evaluate the effect of ketamine on memory consolidation only, ketamine was administered *after* the initial social learning exposure; higher doses could be tested in this paradigm without the drug non-specifically affecting test behavior, since the next social learning exposure was beyond the duration of drug action. When ketamine was administered after initial exposure, memory responses were statistically different between the three dose trials (ANOVA Interval×Trial interaction, $F_{(2,16)}=6.85$, $p=0.007$), with the saline and 10 mg doses showing 'typical' decreases in investigation times of 24.1 s (SD=8.3, $p=0.0003$) and 27.0 s (SD=6.6, $p=0.0003$) but the 30 mg ketamine dose showed no significant memory response (Fig. 3). No differences

were found between experimental groups with regard to initial exploration times in Figs. 2 and 3.

3.3. Chronic antipsychotic effect on social recognition

Chronic treatment with haloperidol (2 mg/kg/day) or olanzapine (4 mg/kg/day) was evaluated for its effect on the ketamine-induced disruption in social recognition. To assure adequate antipsychotic doses in the mice, we prospectively determined the oral subacute dose necessary to achieve human therapeutic plasma levels in mice. After one month of oral drug administration, plasma drug levels in mice were assumed to have achieved the human therapeutic antipsychotic dose range for the two different doses of drug tested (as shown in Table 2 for the two week assessment).

After subchronic antipsychotic drug treatment, social recognition occurred in all mouse groups, represented by a significant drop in exploration time at the "trial" compared with the "initial" exposure in both the APD and water groups ($p<0.0001$ for each of the 6 mouse groups), even though olanzapine, but not haloperidol, modestly but significantly reduced "initial" interaction time (olanzapine "initial" interaction versus the same measure in the water or haloperidol groups, $p=0.01$). Ketamine administration significantly reduced social memory in the water-treated mice ($p=0.003$), consistent with our other results. In addition, the effect of ketamine on social memory was significantly attenuated in the olanzapine- and haloperidol-treated animals, rendering no difference between the mouse-exploration time after saline or ketamine ($p=0.67$ and $p=0.64$, respectively). That is, we observed a difference in memory between saline and ketamine in the water pretreatment group ($p=0.008$ adjusted for multiple testing) but not between water and ketamine in either the haloperidol or the olanzapine pretreatment group ($p>0.60$) (Fig. 4). The three way interaction between ketamine, antipsychotic drug, and social memory was significant in this experiment ($p=0.0124$), showing that ketamine has a significantly different effect on memory behavior in the presence of the antipsychotic drugs versus with water only (Fig. 4). These results show that a first- or a second-generation antipsychotic drug can block the action of ketamine on the disruption of social learning in mice. Of note, these experiments excluded mice who did not meet the 24 second initial exploration criterion; therefore these results can only be generalized to mice which did meet the initial exploration inclusion criterion.

4. Discussion

The results of this study confirm that a C57 mouse can effectively form short- and long-term social memories of another mouse, a behavior previously reported in laboratory rats. The adult C57 mouse recognizes a familiar juvenile when tested at 10–120 min (short-term) or 1–3 days (long-term) after a single 2 min interaction, but loses familiarity with the individual beyond 7 days. The familiarity gained by an adult mouse when exposed to an unfamiliar one is reliable and spontaneous, and it occurs within a few minutes after exposure. This long term memory can be disrupted with blockade of protein synthesis using anisomycin (Kogan et al., 2000). Our results are consistent with reports of learning and recognition in group-housed rodents from other laboratories (Kogan et al., 2000), which showed that the adult rat forms social memories as quickly as 10 min that last for several days after a single exposure. The advantage of demonstrating this behavior in mice derives from the availability of relevant genetically manipulated mouse colonies and the importance of their behavioral characterization.

Ketamine is a PCP congener and a non-competitive antagonist of the NMDA glutamatergic receptor. It disrupts social recognition behavior in the adult mouse. When ketamine was administered before the initial exposure, it disrupted social recognition without significantly influencing the investigatory activity of the mice, confirming our prediction that a drug blocking NMDA-sensitive glutamate transmission would impair social learning. Ketamine induced a selective diminution of longer-term memory (1–3 days) while minimally disrupting short-term (60 min) memory. This latter observation suggests that ketamine did not disrupt acquisition of information to form the memory, only its subsequent consolidation into a longer-term memory construct. This observation suggests that both non-NMDA mediated plasticity as well as NMDA-mediated plasticity is involved in social learning (Sawtell et al., 1999; Volk et al., 2006). Whether a part of this effect of ketamine is due to its actions within the hippocampus has not yet been tested, but it is our speculation, based on the known actions of ketamine in the hippocampus in animals and humans (Gao et al., 1998; Lahti et al., 1995) and hippocampal involvement in social recognition in rats (Kogan et al., 2000). Because blocking transmission at the NMDA receptor disrupts social learning in mice, it is plausible to postulate that some of the manifestations of brain diseases associated with social memory, like schizophrenia or autism, could be associated with altered glutamatergic transmission in brain, possibly in the hippocamal formation.

Ketamine was selected as the NMDA antagonist based on its ability to be used in humans as well as in animal models of psychosis (Lahti et al., 1995). We have already evaluated the ability of MK801 to mimic this ketamine effect on social learning in mice and show that it acts similarly to ketamine, but with greater potency, thus supporting the idea that this disruption of social learning is an NMDA-mediated action. In the data reported here, we show that ketamine when given before the memory acquisition (at 10 mg/kg) was more potent at blocking learning than when given after the acquisition (at 30 mg/kg), even though the ketamine appeared to disrupt memory in both instances. Differential sensitivity to ketamine-induced disruption likely represents a complex interaction between neurocircuitry and neuropharmacology active in the acquisition of a memory versus that involved in memory consolidation. The relative balance of NMDA involvement may be weighted more towards acquisition than consolidation (Lynch, 1998; Riedel et al., 2003) or differentially involved in unique forms of memory consolidation (i.e. specific to social recognition) (Nadel and Bohbot, 2001).

The two antipsychotics, representative of the first and second generation drugs, alone failed to modify social learning in mice. This suggests that antipsychotic drugs could be devoid of adverse actions on social memory in humans, an observation already suggested in human studies (Green, et al., personal communication). Because these medications have adverse effects on other aspects of memory (Reilly et al., 2006), this sparing of social memory could be of clinical significance. Moreover, given the importance of social memory in overall psychosocial recovery in a psychotic illness like schizophrenia (Green, 1996), it is important that treatments for the illness do not worsen important domains of function in persons with the illness.

Antidopaminergic drugs, especially the second generation compounds, have been shown to block the actions of NMDA antagonists on animal behavior (Corbett et al., 1995; Hoffman, 1992) and neurochemistry (Sharp et al., 1992; Nakki et al., 1996; Sharp et al., 1991). First and second generation antipsychotic drugs antagonize MK801 induced locomotion (Corbett et al., 1995; Hoffman, 1992; Terranova et al., 2005) and stereotypic behaviors (Tiedtke et al., 1990; Arvanov et al., 1997). Clozapine and olanzapine but not haloperidol antagonized PCP-induced social withdrawal in nonhuman primates (Corbett et al., 1995). Arvanov et al. (1997) showed that olanzapine and clozapine, but not haloperidol, can facilitate glutamatergic transmission and block PCP effects on NMDA-mediated electrophysiologic responses in the medial PFC of rats (Svensson, 2000; Ninan et al., 2003). Thus, antipsychotic drugs can attenuate some but not all behavioral effects of NMDA receptor antagonists. It is often assumed that the differences between the first and second generation of medications are due to the greater serotonin antagonism of later group of drugs, whereas their common actions are due to dopaminergic blockade.

It is not surprising therefore that the antipsychotic drugs blocked ketamine effects on social behavior. The present data demonstrate that both a first (haloperidol) and second (olanzapine) generation antipsychotic drug can antagonize ketamine-induced disruption on social memory. This observation suggests that the dopamine antagonism of these drugs (i.e., their common mechanism) is more important in blocking the ketamine effect than the serotonin antagonism (i.e., an action relatively distinctive to olanzapine). Because the literature more often reports that olanzapine is more effective in blocking social and NMDA-mediated behaviors than haloperidol, it is somewhat surprising that we have shown an equivalent action in this paradigm between both drugs. The explanation may lie in a species difference since most studies were done in rats or it may be a function of the task since this is the first report of antipsychotic efficacy in a social recognition task. Recent studies conducted in C57BL/6J mice in our lab (unpublished) show equivalent efficacy for haloperidol, olanzapine and clozapine in ameliorating this ketamine action implicating antipsychotic drug efficacy in improving social recognition and memory. Although the mechanism of action of these antipsychotics on ketamine-induced behaviors is unknown and may be indirect, we propose that it is mediated by dopamine receptor blockade. If the site of ketamine action is in the hippocampus, the possibility exists that these two drugs act at D4 dopamine receptors, given the substantial density of the dopamine D4 receptor in the hippocampal formation (Lahti et al., 1998; Browman et al., 2005). Alternatively, antidopaminergic agents could act within the striatum to attenuate ketamine effects in distal structures mediated through long tract or distant circuit connections (Lisman and Grace, 2005; De Leonibus et al., 2006). Charara and Grace suggest that dopamine in the striatum modulates hippocampal function through long tract projections, shuttering hippocampal influence on the prefrontal cortex (Charara and Grace, 2003). Otmakhova and Lisman have shown a dopaminergic influence on the Schaffer Collateral projections to CA1 within the hippocampus most likely mediated by the D5 dopamine receptor (Otmakhova and Lisman, 1999).

In summary, we have confirmed the existence of social memory in mice using an established behavioral paradigm, the disruption of this memory with ketamine and its restitution with antipsychotic drugs, thus, providing new and pertinent pharmacological characterization of this behavior. Because of the demonstrated role of hippocampus in social memory and the known pharmacologic actions of NMDA blockade in the hippocampus, we postulate that this ketamine-induced effect may be mediated by its hippocampal actions. Whether the "corrective" action of antipsychotics, among several different possibilities, is a direct action in hippocampus or an effect mediated by long tract neural systems from striatum is unknown but could be further tested. These data suggest that social learning and memory examined with the described paradigms may prove to be a useful animal behavior in the study of hippocampal function and pharmacology (Storm and Tecott, 2005) and, potentially, to study mechanisms of social cognition.

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