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MK-801 produces a deficit in sucrose preference that is reversed by clozapine, D-serine, and the metabotropic glutamate 5 receptor positive allosteric modulator CDPPB: Relevance to negative symptoms associated with schizophrenia?

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ABSTRACT

Currently prescribed antipsychotics attenuate the positive symptoms of schizophrenia but fail or only mildly improve negative symptoms. The present study aimed to establish an animal model of negative symptoms by examining the effects of the NMDA receptor antagonist MK-801 on sucrose preference. We sought to validate the model by examining the effects of clozapine and D-serine, for which there are positive clinical data regarding their effects on negative symptoms, and haloperidol which is clinically ineffective. We extended our analysis by examining CDPPB, an mGlu5 receptor positive allosteric modulator. Acute MK-801 produced effects indicative of a shift in the hedonic experience of sucrose not confounded by disruptions in motor abilities or taste as revealed by: 1) a decrease in sucrose intake at low concentrations (0.8% or 1.2%), but no effect on water, 2) an increase in consumption for higher (7%) sucrose concentrations, reflecting a shift to the right in the concentration–consumption curve, and 3) no effect on quinine intake. Sub-chronic clozapine and acute D-serine attenuated the MK-801-induced deficit in 1.2% sucrose consumption, whereas sub-chronic haloperidol (0.02 mg/kg) did not. Finally, acute treatment with CDPPB also attenuated this deficit. These data suggest that this model may be useful for identifying novel agents that improve negative symptoms, and that compounds which enhance NMDA receptor function, such as mGlu5 receptor PAMs, may have clinical utility in this regard.

1. Introduction

Currently prescribed antipsychotics are effective at alleviating the positive symptoms of schizophrenia, but fail or only mildly improve the cognitive deficits and negative symptoms associated with this disease. This may be due to the fact that most antipsychotics share a common mechanism of action, namely D2 dopamine receptor antagonism (Kapur and Mamo, 2003; Seeman et al., 1975; Seeman and Lee, 1975). It has been suggested that dopamine hyperfunction, particularly in the limbic region, may be involved in positive symptoms whereas the cognitive deficits and negative symptoms may be related to NMDA receptor dysfunction (Coyle and Tsai, 2004). Thus, in contrast to amphetamine administration, which enhances dopamine efflux and produces positive-like symptoms in normal individuals, NMDA receptor antagonists such as PCP and ketamine produce not only positive symptoms, but cognitive deficits and negative symptoms as well (Javitt, 1987; Krystal et al., 1994; Steinpress, 1996).

In light of recent evidence indicating that cognition and negative symptoms are better predictors of functional outcome than positive symptoms (Bowie et al., 2006; Green, 1996; Harvey et al., 2006), it has become clear that there is a need for treatments that have greater symptom coverage. One target showing potential for greater coverage is the metabotropic glutamate 5 (mGlu5) receptor. mGlu5 is a Gq coupled receptor, for which activation has been reported to enhance NMDA receptor functioning (Awad et al., 2000; Liu et al., 2006). Furthermore, administration of the mGlu5 positive allosteric modulator CDPPB attenuated amphetamine-induced locomotor activity (Liu et al., 2008) as well as PCP- and MK-801-induced deficits in set-shifting and novel object recognition (Darrah et al., 2008; Uslaner et al., 2009), assays believed to be sensitive to antipsychotic-like and cognition enhancing compounds, respectively. In the present study we aimed to characterize the potential of CDPPB for treating the negative symptoms associated with schizophrenia.

Given that anhedonia (diminished experience of pleasure) is a core component of negative symptoms (Kirkpatrick and Buchanan, 1990; Kontaxakis et al., 2006; Loas et al., 1996; Park et al., 2009), and that acute NMDA receptor antagonism produces blunted affect in humans (Krystal et al., 2005; Vollenweider et al., 1997), we characterized the effects of acute NMDA receptor antagonism via MK-801 administration on sucrose preference in rats, a preclinical measure of

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hedonia (Muscat et al., 1992). Previous studies have shown that chronic stress induces deficits in sucrose preference, which is reversed by antidepressants (Marona-Lewicka and Nichols, 1997; Willner et al., 1987) and withdrawal from PCP produces deficits that are attenuated by clozapine but not haloperidol (Turgeon and Hulick, 2007). We further validated the assay by characterizing the effects of clozapine and D-serine, both of which have shown clinical efficacy in patients (Brar et al., 1997; Javitt, 2001; Meltzer, 1992; Tsai et al., 1998), as well as haloperidol, which is clinically ineffective (Borison, 1995; Purdon et al., 2001; Schooler, 1994). Finally, we report that activation of mGlu5 receptors with CDPPB also significantly attenuated the MK-801-induced deficit in sucrose preference. These collective findings are particularly exciting because they suggest that activation of mGlu5 receptors has the potential to treat not only the positive and cognitive symptoms associated with schizophrenia, but perhaps negative symptoms as well.

2. Methods

2.1. Subjects

Adult male Wistar–Hannover rats (Charles River Laboratories, Wilmington, MA) weighing 250–300 g were used in all experiments. Animals were single-housed upon arrival and maintained on a 12 h light/dark cycle. Food was available *ad libitum*, and two adjacent bottles containing water were maintained atop the cages at all times for the first week after arrival (see below for more detail). All experimental procedures were approved by the Institutional Animal Care and Use Committee and conducted in accordance with the National Institutes of Health guide for the care and use of laboratory animals.

2.2. Drugs

3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (CDPPB) was synthesized in-house similar to the procedures described by Lindsley et al. (2004), suspended in 0.5% methylcellulose, and dosed intraperitoneally at 2 mL/kg. (+)-MK-801 hydrogen maleate (0.3 mg/kg) and quinine hydrochloride dihydrate (0.3 mM) were obtained from Sigma Aldrich (St. Louis, Missouri), and (+)-MK-801 was administered intraperitoneally at 1 mL/kg in saline. D-Serine (1280 mg/kg) was obtained from Fisher Scientific (Norristown, PA) and was dosed subcutaneously at 5 mL/kg in saline. Clozapine (3 mg/kg) and haloperidol (0.02 mg/kg) were obtained from Fisher Scientific (Norristown, PA) and were administered subcutaneously at 1 mL/kg in 2% glacial acetic acid after the pH had been adjusted to ~5. The doses of D-serine and CDPBB were chosen based on their ability to reverse MK-801-induced cognitive deficits at these doses (Smith et al., 2008; Uslaner et al., 2009). The doses of clozapine and haloperidol that were chosen are approximately one-third the effective dose for reducing amphetamine- and MK-801-induced locomotor activity (in-house data and see (Natesan et al., 2008)) and one-third the dose that produces clinically relevant D2 receptor occupancy (Kapur et al., 2003). Higher doses of haloperidol and clozapine were not used because they reduce spontaneous motor activity which could disrupt liquid consumption.

2.3. Sucrose preference tests

Following one week of acclimation to the animal colony room, animals underwent a daily schedule of 20 h water deprivation which lasted for the duration of the experiment. Water was made available for 4 h daily and sucrose solution was additionally available for the first hour of this window. For this first hour (testing period), two pre-weighed test bottles were placed on each animal's cage in the same location as the water bottles to which the animal had been habituated. One bottle contained a sucrose solution and the other contained water. Daily placement of the bottles on the left or right sides was randomly determined, and bottle locations were switched halfway through the 1-hour exposure period. Following testing, bottles were removed and re-weighed, and sucrose and water consumption were calculated. The bottles used for testing were immediately replaced with water bottles, and water was made available for an additional 3 h. All groups were counterbalanced and pseudo-randomized according to sucrose and water consumption. No significant differences in bodyweight existed between groups when assigned to treatment conditions, and none emerged following chronic drug administration.

2.4. The effects of MK-801 on sucrose and quinine consumption

Twenty-five subjects underwent sucrose testing as described above until a stable preference baseline was reached, at which time animals were pseudo-randomly assigned to two groups such that mean fluid consumption baselines were similar. Group 1 received 7% sucrose solution and group 2 received 0.8% sucrose solution. Each group was further sub-divided into a group receiving MK-801 (0.3 mg/kg, i.p. in saline) or vehicle 30 min prior to testing.

A separate group of fifty rats was instead given access to 0.3 mM quinine solution in place of sucrose for seven days (1 h/day followed by 3 h of only water). The concentration of quinine chosen for this experiment was based on previously published data showing that 0.3 mM quinine produces a rather mild aversion (Baird et al., 2008; Shimura et al., 2002). Thirty rats demonstrated stable quinine aversion (i.e. water preference), and these animals were pseudo-randomly assigned into three test groups ($n=10$) such that mean fluid consumption baselines were equal. On test day, animals were given injections of MK-801 (0.3 mg/kg i.p., 1 mL/kg in saline) or vehicle 30 min prior to testing. Quinine aversion was measured in the same manner as sucrose preference.

2.5. The effects of acute and sub-chronic clozapine and sub-chronic haloperidol on the MK-801-induced deficit in sucrose consumption

Baseline consumption was established as described above and animals were pseudo-randomly assigned into three test groups ($n=6$) such that mean fluid consumption baselines were equal. Animals were given clozapine (3 mg/kg, sc, 1 mL/kg in 2% glacial acetic acid) or vehicle 60 min prior to testing, followed by MK-801 (0.3 mg/kg i.p. in saline) or vehicle 30 min prior to testing. Thus, on day 1, group 1 received two doses of vehicle, group 2 received vehicle followed by MK-801, and group 3 received clozapine followed by MK-801. On the next day and for the following eight consecutive days, groups 1 and 2 received vehicle b.i.d. and group 3 received clozapine (3 mg/kg) b.i.d. Testing with MK-801 was performed again on the final day of dosing (day 10) with group 1 receiving two doses of vehicle, group two receiving vehicle followed by MK-801, and group 3 receiving clozapine followed by MK-801 in the same manner as before. Sucrose concentrations were set at 1.2% for this and all following experiments, as this concentration was found to more quickly result in stable baselines and stronger preference (as compared to 0.8% sucrose solution).

A separate cohort of animals were pseudo-randomly assigned into three test groups ($n=10$) in the same way, and were then given haloperidol (0.02 mg/kg sc, 1 mL/kg in 2% glacial acetic acid) or vehicle b.i.d. for 9 consecutive days and testing was performed on the final day of dosing (day 10).

2.6. The effects of acute D-serine on the MK-801-induced deficit in sucrose consumption

Baseline consumption was established as described above and animals were pseudo-randomly assigned into three test groups ($n=10$)

such that mean fluid consumption baselines were equal. Animals were given D-serine (1280 mg/kg sc, 5 mL/kg in saline) or vehicle 1 h before injections of MK-801 (0.3 mg/kg i.p., 1 mL/kg in saline) or vehicle. Testing began 30 min following injections of MK-801.

2.7. The effects of acute CDPPB on the MK-801-induced deficit in sucrose consumption

Baseline consumption was established as described above and animals were pseudo-randomly assigned into three test groups ($n=10$) such that mean fluid consumption baselines were equal. Animals were given CDPPB (3 mg/kg i.p., 2 mL/kg in 0.5% methylcellulose) or vehicle 30 min before injections of MK-801 (0.3 mg/kg i.p., 1 mL/kg in saline) or vehicle. Testing began 30 min following injections of MK-801.

2.8. Statistics

The interaction between sucrose concentration and MK-801 on sucrose and water consumption was analyzed using two-factor ANOVA (concentration × treatment) and effects of MK-801 on sucrose and water consumption were then analyzed separately using independent sample *t*-tests. Effects of MK-801 on quinine vs water were analyzed with separate *t*-tests. All other experiments were analyzed using one-way ANOVA followed by Fischer's LSD post-hoc tests to examine group differences, and data transformations were deemed unnecessary following Shapiro–Wilk tests for skewness. Although it is true that multiple experiments were performed, increasing the number of comparisons and the likelihood of Type I error, adjusting alpha for comparisons made in independent experiments is not the general practice and therefore was not employed.

3. Results

3.1. The effects of MK-801 on sucrose and quinine consumption

The influence of MK-801 on sucrose consumption was found to significantly differ as a function of sucrose concentration (Fig. 1). ANOVA revealed a significant interaction between MK-801 treatment and sucrose concentration ($F_{(1,\ 16)}=52.20$, $p<0.001$). MK-801 significantly increased consumption of the high (7%) concentration solution ($p<0.001$), but decreased consumption of the lower (0.8%) solution ($p=0.015$). There was no effect of MK-801 on water consumption.

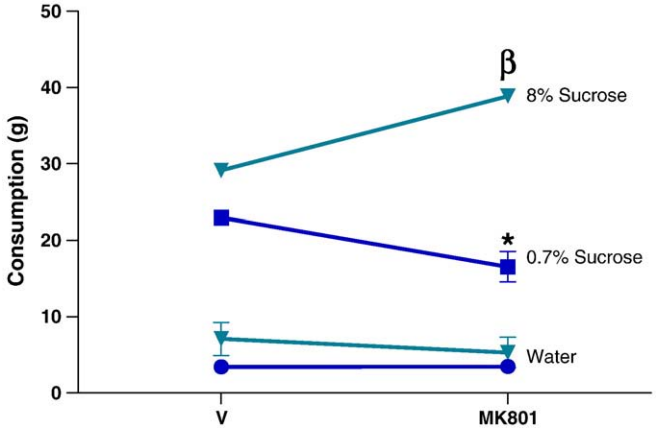

Fig. 1. Effect of MK-801 on sucrose consumption as a function of percent sucrose and treatment. * indicates consumption significantly lower than vehicle; β indicates consumption significantly higher than vehicle. $N=5$/group.

For animals given the choice between water and quinine, MK-801 significantly decreased water consumption ($t=0.05$, $p=0.035$) but had no effect on quinine consumption (Fig. 2).

3.2. The effects of acute and sub-chronic clozapine and sub-chronic haloperidol on the MK-801-induced deficit in sucrose consumption

Acute dosing with MK-801 decreased sucrose consumption in both vehicle and clozapine pretreated groups, relative to the group not receiving MK-801 (main effect of group, $F_{(2,\ 15)}=11.78$, *p*-value for all MK-801-treated groups <0.01; Fig. 3). Animals pre-treated with acute clozapine showed a slight trend toward reversal of the MK-801 effect, but results were not significant. There was no effect of MK-801 on water consumption.

After receiving clozapine (3 mg/kg) or vehicle b.i.d. for 10 days, all animals treated with MK-801 on day 10 exhibited significantly lower sucrose intake than vehicle treated animals (main effect of group, $F_{(2,\ 15)}=17.70$, *p*-value for each MK-801-treated group ≤ 0.01). Importantly, however, clozapine attenuated the MK-801 effect as revealed by a significant difference between animals receiving sub-chronic clozapine prior to MK-801 vs sub-chronic vehicle prior to MK-801 ($p<0.01$; Fig. 4). There was no effect of MK-801 on water consumption.

After b.i.d. dosing for 10 days with 0.02 mg/kg haloperidol or vehicle, all animals treated with MK-801 on day 10 exhibited significantly lower sucrose intake than vehicle treated animals (main effect of group, $F_{(2,\ 25)}=10.24$, *p*-value for each MK-801-treated group <0.01; Fig. 5). Pre-treatment with haloperidol had no effect on the MK-801-induced deficit. There was no effect of MK-801 or haloperidol on water consumption.

3.3. The effects of acute D-serine on the MK-801-induced deficit in sucrose consumption

MK-801 decreased sucrose, but not water consumption for all groups relative to vehicle (main effect of group, $F_{(2,\ 24)}=22.67$, *p*-value for each MK-801-treated group <0.001). However, acute treatment with 1280 mg/kg D-serine significantly attenuated the MK-801-induced deficit ($p=0.005$; Fig. 6). There was no effect of D-serine on water consumption.

3.4. The effects of acute CDPPB on the MK-801-induced deficit in sucrose consumption

MK-801 decreased sucrose, but not water consumption for all groups relative to vehicle (main effect of group, $F_{(2,\ 58)}=9.008$, $p<0.001$, *p*-value for each MK-801-treated group <0.05). Importantly,

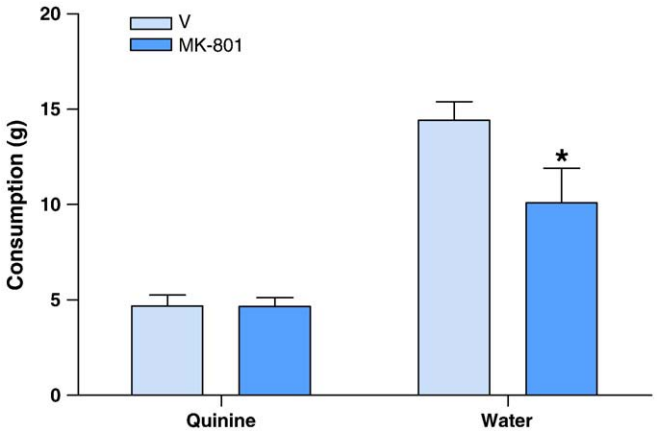

Fig. 2. Difference in quinine and water consumption as a function of vehicle or MK-801. * indicates consumption significantly lower than vehicle.

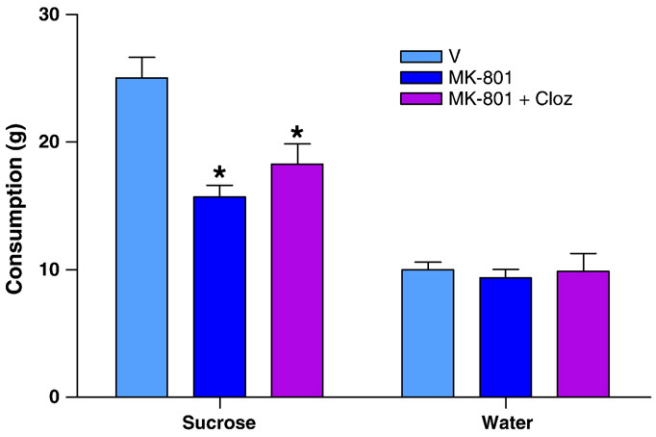

Fig. 3. Influence of MK-801 (0.3 mg/kg) and clozapine (3 mg/kg) on water and sucrose consumption after clozapine was given acutely. * indicates consumption significantly lower than V. $N = 6$/group.

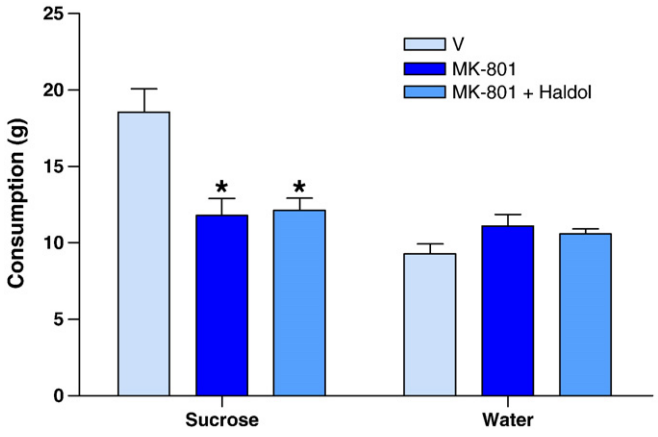

Fig. 5. Influence of MK-801 (0.3 mg/kg) and haloperidol (0.02 mg/kg) on water and sucrose consumption after haloperidol was given BID for 10 days.* indicates consumption significantly lower than vehicle. $N = 10$/group.

a single injection of 3 mg/kg CDPPB significantly reversed the MK-801-induced deficit ($p = 0.045$; Fig. 7). CDPPB had no effect on water consumption.

4. Discussion

Although clinically available antipsychotics have therapeutic effects against positive symptoms, current treatments for schizophrenia are inadequate at improving the negative symptoms associated with the disease. The reason why little progress has been made on this front may be partially due to the relatively few validated preclinical assays for assessing negative symptoms, making drug development more difficult (but see Sams-Dodd, 1998; Turgeon and Hulick, 2007). Given that acute administration of the NMDA receptor antagonists PCP and ketamine to humans produces effects similar in nature to negative symptoms, we examined the acute effects of the NMDA receptor antagonist MK-801 on sucrose preference.

We report that MK-801 disrupts sucrose preference when relatively low sucrose concentrations are available, but increases preference for higher sucrose concentrations. This apparent discrepancy seems at odds with the suggestion that MK-801 disrupts the hedonic value of sucrose. However, the concentration–consumption curve for sucrose is not linear but rather follows an inverted-U shaped concentration–effect function. Specifically, at lower concentrations (below ~5%) consumption increases with concentration, but actually declines when higher sucrose concentrations are made available (Shimura et al., 2002; Towell et al., 1987). Thus, 7% sucrose, while being more preferred than 0.8% as indicated by higher overall consumption (Figs. 1 and 2), is on the descending limb of the concentration–consumption function. As a result, a treatment that disrupts the hedonic value of sucrose would be expected to increase consumption of higher sucrose concentrations by shifting the concentration–consumption curve to the right. Further supporting this hypothesis, Spielewoy and Markou (2003) have shown that withdrawal from the NMDA receptor antagonist PCP, which might better model certain aspects of schizophrenia than acute treatment (Jentsch and Roth, 1999), induces a right-ward shift in intracranial self-stimulation threshold, an alternative measure of reward value.

It is well known that MK-801 can affect locomotor activity, which has the potential to interfere with fluid intake. However, several findings suggest that the effects on sucrose consumption produced by MK-801 are not simply due to a motor impairment. First, one would expect a disruption in consumption independent of sucrose concentration if the deficit were due to a motor impairment. This was not the case — consumption of higher concentrations was actually increased by MK-801 administration. Furthermore, under conditions in which sucrose was available, MK-801 did not affect water consumption. If a motor impairment was the cause of the decrease in sucrose consumption (at lower concentrations), one would also expect the motor impairment to affect water consumption.

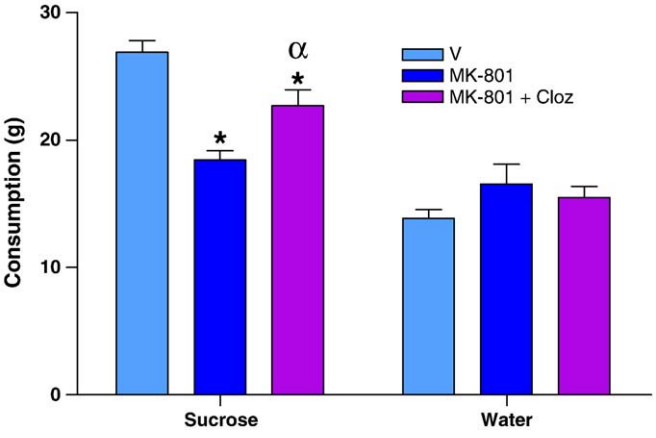

Fig. 4. Influence of MK-801 (0.3 mg/kg) and clozapine (3 mg/kg) on water and sucrose consumption after clozapine was given BID for 10 days. * indicates consumption significantly lower than V; α indicates consumption significantly greater than MK-801. $N = 6$/group.

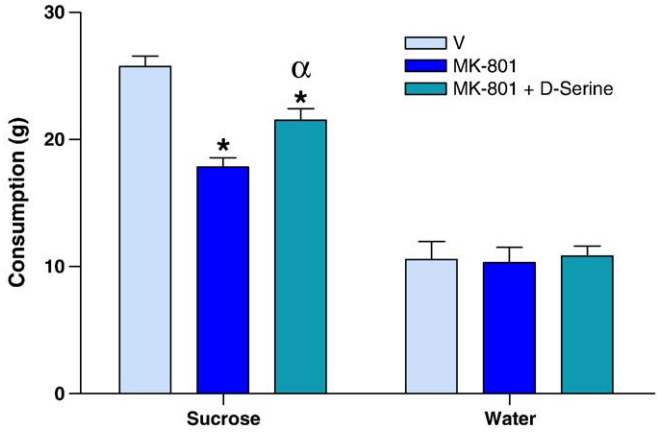

Fig. 6. Influence of MK-801 (0.3 mg/kg) and acute D-serine (1.28 g/kg) on water and sucrose consumption. * indicates consumption significantly lower than vehicle; α indicates consumption significantly greater than MK-801. $N = 10$/group.

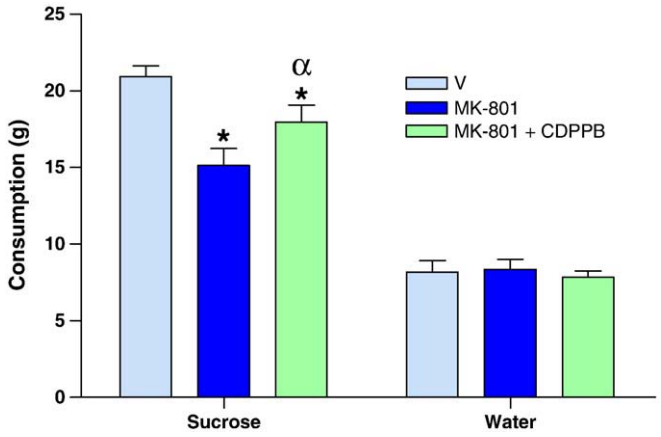

Fig. 7. Influence of MK-801 (0.3 mg/kg) and CDPPB (3 mg/kg) on water and sucrose consumption. * indicates consumption significantly lower than vehicle; α indicates consumption significantly greater than MK-801. $N = 10$/group.

A second potential confound that could explain our data is that MK-801 might impair the sensory experience of tastants, rather than their hedonic impact. That is, if MK-801 were simply blunting the sensory experience of sucrose this could potentially explain the shift to the right in the concentration–consumption curve for sucrose. In order to address this possibility, we examined the effects of MK-801 on quinine aversion. We hypothesized that if the effects of MK-801 on sucrose consumption were the result of diminished taste sensitivity, one would expect MK-801 to increase quinine consumption by decreasing its aversive qualities. On the other hand, if the MK-801 impairment in sucrose consumption was due to a shift in the hedonic experience of sucrose, one might predict that it would reduce water consumption more extensively than quinine, given that water is the more preferred solution under this protocol (i.e. in the same way MK-801 impaired sucrose but not water consumption when sucrose was the more preferred solution). The results from this experiment were unequivocal — MK-801 decreased water consumption but had no effect on quinine consumption.

Given the results from the first experiments, we attempted to further validate this assay as a preclinical measure of negative symptoms by characterizing the effects of clozapine and D-serine, for which there is limited positive clinical data associated with negative symptoms (Brar et al., 1997; Javitt, 2001; Meltzer, 1992; Tsai et al., 1998), and haloperidol, for which most clinical data is negative (Borison 1995; Purdon et al., 2001; Schooler 1994). Both clozapine and D-serine were found to partially attenuate the effects of MK-801, clozapine being active only after repeated dosing as has been reported previously using PCP withdrawal to produce a deficit in sucrose preference (Turgeon and Hulick, 2007). In contrast, repeated administration of haloperidol failed to have an effect. These findings indicate the potential utility of this assay for identifying compounds with therapeutic effects against negative symptoms.

Of course these conclusions are tempered somewhat by the fact that only one dose of D-serine, clozapine, and haloperidol was examined. The dose of D-serine was chosen based on our previous findings that it attenuates the psychostimulant effects of amphetamine and reverses an MK-801-induced deficit in novel object recognition (Smith et al., 2008; Uslaner et al., 2009). The doses of haloperidol and clozapine were chosen because they are approximately one-third the effective dose for attenuating amphetamine- and MK-801-induced locomotor activity (in-house data and Natesan et al., 2008) and one-third the dose that produces clinically relevant D2 receptor occupancy (Kapur et al., 2003). It will be valuable in the future to examine additional doses of these compounds to determine the shape of their respective dose–effect curves.

Finally, we extended the characterization of this assay by examining the effects of CDPPB, an mGlu5 PAM that has been shown to enhance NMDA receptor function and also shown to have effects in assays measuring antipsychotic potential (Liu et al., 2008) and cognitive improvement (Uslaner et al., 2009) The dose we chose to examine here was based on our previous cognition results (Uslaner et al., 2009). Similarly to what was found with D-serine, acute CDPPB administration partially reversed the deficit in sucrose consumption produced by MK-801.

It is interesting to speculate on the mechanisms underlying the effects of CDPPB, D-serine, and clozapine on sucrose preference. For CDPPB and D-serine, it seems likely that NMDA receptor functioning might be involved. Activation of mGlu5 *in vitro* increases NMDA receptor mediated current (Awad et al., 2000; Doherty et al., 1997), as well as NMDA-dependent long-term potentiation in hippocampal slices (Kotecha et al., 2003) and phosphorylation of the NMDA receptor subunit NR1 (Liu et al., 2006; Uslaner et al., 2009). D-serine also affects NMDA receptor function by acting as a co-agonist on the receptor. The NMDA receptor requires the presence of both agonist (glutamate) and co-agonist (glycine, D-alanine, and/or D-serine) for the ligand-gated ion channel to open (Johnson and Ascher, 1987; Kemp and Leeson, 1993; McBain et al., 1989; Mothet et al., 2000), and D-serine administration has been found to enhance both NMDA receptor current (Guo et al., 2005; Martina et al., 2003) and NMDA receptor-dependent long-term potentiation (Oliver et al., 1990; Yang et al., 2003). Thus, we speculate that CDPPB and D-serine may increase sucrose preference by enhancing NMDA receptor functioning, consistent with the hypothesis that NMDA receptor dysfunction might underlie negative symptomatology.

In contrast to D-serine and CDPPB, the neuronal mechanisms underlying the effects of clozapine are more difficult to pinpoint. Clozapine has a somewhat promiscuous and unique pharmacological profile, including a higher affinity for the 5-HT2A receptor relative to the D2 receptor compared to most other antipsychotics (Meltzer et al., 1989), 5-HT1A receptor agonism (Rollema et al., 1997), and a relatively high affinity/potency for several muscarinic receptors (Michal et al., 1999; Olianas et al., 1997; Zeng et al., 1997; Zorn et al., 1994). Although this receptor profile may certainly contribute to the effects reported here, clozapine also has effects on glutamate release, as well as on NMDA receptor expression and activity (Fitzgerald et al., 1995; Gemperle and Olpe, 2004; Yamamoto et al., 1994). Interestingly, some of the effects produced by clozapine, including a reduction in the glutamate transporters GLT-1 (Bragina et al., 2006; Melone et al., 2001), EAAT2 and EAAT3 (Schmitt et al., 2003), only occur after sub-chronic treatment. Reductions in these transporters would be expected to increase synaptic glutamate concentration and NMDA receptor functioning. Furthermore, these plastic changes that occur only after sub-chronic treatment might underlie the differential effects on sucrose consumption when clozapine was administered acutely vs sub-chronically. Finally, some of the abovementioned neurobiological effects produced by clozapine do not occur following haloperidol treatment (for review, see Millan, 2005), thus possibly explaining the lack of effects observed with haloperidol both in this study and in clinical studies measuring efficacy against negative symptoms.

In conclusion we have validated the use of an MK-801 deficit in sucrose preference as a promising means to measure the therapeutic potential of compounds for treating negative symptoms. The deficit is reversed by the clinically effective compounds clozapine and D-serine, but not by the clinically ineffective compound haloperidol, albeit only a single dose of haloperidol was examined. Furthermore, the mGluR5 PAM, CDPPB also attenuated the MK-801 deficit in sucrose consumption, suggesting that mGluR5 activation might have therapeutic potential for treating negative symptoms. This finding is particularly exciting given that we and others have previously shown that mGluR5 activation has antipsychotic-like activity and cognition enhancing

effects in other preclinical assays. We hypothesize that mGluR5 PAMs will have broader symptom coverage than currently available antipsychotics, fulfilling an unmet medical need.

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