Pharmacology, Biochemistry and Behavior 95 (2010) 203–208

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Memantine improves memory for taste-avoidance learning in day-old chicks exposed to isolation stress☆

Teresa A. Barber *, Ryan A. Meyers [1], Brian F. McGettigan [2]

Department of Psychology, Dickinson College, Carlisle, PA 17013, United States

ARTICLE INFO

Article history:
Received 8 September 2009
Received in revised form 8 January 2010
Accepted 18 January 2010
Available online 25 January 2010

Keywords:
Chickens
Memantine hydrochloride
Receptors
N-Methyl-D-aspartate
Learning
Memory

ABSTRACT

Activation of NMDA receptors by glutamate is particularly important in the initial stages of memory consolidation. Memantine, a noncompetitive NMDA receptor antagonist, ameliorates memory impairment under certain circumstances, despite blocking the activation of NMDA receptors. The present experiments tested the hypothesis that memantine can improve memory deficits induced by isolation stress in day-old chicks (*Gallus gallus domesticus*) trained in a one-trial taste-avoidance task. Three experiments assessed the effects of memantine at different concentrations and in combination with isolation stress. The results of Experiment 1 indicate that, under normal, non-stressed conditions, memory in control animals is strong and 15.0 mM memantine impairs memory, similar to that seen in many studies of the effects of NMDA receptor antagonists on learning. However, the results of Experiments 2 and 3 showed that, when chicks were exposed to isolation stress during the pre-training period, memory formation for saline-injected control animals was impaired and 5.0 mM memantine significantly improved memory in an inverted U-shaped dose response function. The current results extend the findings that memantine can ameliorate memory impairment and supports the hypothesis that memantine, despite its action to reduce NMDA receptor activity, can facilitate normalized memory acquisition.

1. Introduction

The neurotransmitter glutamate and its receptors, in particular the N-methyl-D-aspartate (NMDA) subtype, are important for learning of new information. Morris et al. (1986) were first to demonstrate that AP-5, a competitive NMDA receptor antagonist, impaired spatial learning in rats, at doses comparable to those that impaired long-term potentiation in the hippocampus, a process and site shown to be important for learning the task (see Lynch, 2004). Since this time, many researchers have confirmed that NMDA receptor blockers impair memory formation in many species and paradigms (Butelman, 1989; Misztal and Danysz, 1995; Roberts and Shapiro, 2002; Sanger, 1992; Ungerer et al., 1991; Watson and Stanton, 2009; Xu, 1997; see Robbins and Murphy, 2006).

In recent years, research has focused on the effects of memantine, a noncompetitive NMDA receptor antagonist approved in 2003 for the treatment of moderate to severe Alzheimer's disease (Chen and Lipton, 2006; Doody et al., 2007; see Parsons et al., 2007). In contrast to the effects of most NMDA receptor antagonists, memantine has been demonstrated to improve learning in a variety of paradigms; improvement is seen when memory formation has been challenged in some way, such as that seen in Alzheimer's disease (AD) or the application of amnestic substances or procedures (Camarasa et al., 2008; Zajaczkowski et al., 1997).

The chick one-trial taste-avoidance learning task is a perfect paradigm in which to study the effects of NMDA receptor antagonists such as memantine. In this task, chicks are trained to peck brightly colored beads coated with an aversant such as methylanthranilate (MeA). At training, the chicks display a disgust response, consisting of head-shaking and beak-wiping. The animals learn to avoid beads that are similar in appearance to the one presented at training during subsequent testing trials (see Gibbs et al., 2008; Rose, 2000). This one-trial learning task results in testable retention lasting at least 24 h, accompanied by discrete biochemical and physiological consequences localized to areas of the chick forebrain (Rose, 2004).

Memory formation for taste-avoidance learning is dependent on NMDA receptor activity. The brain of the day-old chick is rich in NMDA receptors, especially in the hippocampus and intermediate medial mesopallium (IMM), areas critical for learning the taste-avoidance task (Mitsacos et al., 1990; Patterson et al., 1990; Patterson

☆ Teresa A. Barber has previously published as Teresa A. Patterson. Preliminary results from this paper have been published at Society for Neurosciences Annual Meeting (Barber, T. A., McGettigan, B. F., and Meyers, R.A. (2002). The effects of memantine on memory formation for passive avoidance learning in day-old chicks. *Society for Neuroscience Abstracts*, 28, 684.6). This work was supported by internal funding from Dickinson College.

* Corresponding author. Department of Psychology, Dickinson College, PO Box 1773, Carlisle, PA 17013-2896, United States. Tel.: +1 717 245 1641; fax: +1 717 245 1995.
E-mail address: barber@dickinson.edu (T.A. Barber).
[1] Present address: Department of Psychology, Arizona State University, 950 S. McAllister, Tempe, AZ, 85287-1104, United States.
[2] Present address: Department of Otolaryngology, Jefferson Medical College, Thomas Jefferson University, 925 Chestnut St. 6th Floor, Philadelphia, PA 19107-5587, United States.

0091-3057/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2010.01.006

and Rose, 1992; Rose, 2000; Sandi et al., 1992). Memory formation in this task is associated with an increase in the amount of extracellular glutamate in the IMM, increases in the levels of NMDA receptor activation and binding of glutamate, and activation of pre- and post-synaptic calcium channels mediated through NMDA receptor activation (Daisley and Rose, 2002; Salinska et al., 1999; Steele et al., 1995; Stewart et al., 1992). Injections of glutamate or NMDA receptor antagonists generally produce amnesia in the taste-avoidance task (Burchuladze and Rose, 1992; Ng et al., 1997; Patterson et al., 1986; Rickard et al., 1994; Sherry and Crowe, 2008).

Of interest to this study, social isolation stress is one design manipulation that significantly alters learning in the taste-avoidance task. Chicks are social by nature, and separation produces behavioral signs of stress, including an increase in distress calls and frequency of escape behaviors (Bermant, 1963; Rajecki et al., 1977). Social isolation also increases corticosterone levels compared to group-housed and pair-housed animals for at least 15 min following separation (Feltenstein et al., 2003; Johnston and Rose, 1998; Jones and Merry, 1988). Studies with mammals have shown that corticosterone increases glutamate activity, including rapid increases of NMDA-induced $Ca2^{+}$ elevation and increases in glutamate levels in the hippocampus (Abrahám et al., 1996; Liu et al., 2007; Lowy et al., 1993; Moghaddam et al., 1994; Sato et al., 2004).

Stress modulates memory formation for taste-avoidance learning. Corticosterone injection produces amnesia for the task (Sandi and Rose, 1997). On the other hand, corticosterone (Sandi and Rose, 1994) or social isolation stress (Johnston and Rose, 1998) enhance learning of a weak version of the taste-avoidance task, in which diluted concentrations of MeA are used and memory does not last very long. MK801, a NMDA receptor antagonist, abolished the enhancement of memory formation produced by corticosterone, suggesting that corticosterone might act on memory formation through its action on NMDA receptor activity (Venero and Sandi, 1997).

The evidence suggests that social isolation induces changes in the levels of corticosterone, which might, in turn, act through the glutamate receptor to modulate memory formation in the day-old chick. In a weak version of the task, corticosterone acts to improve memory, whereas it produces impairment of memory for the strong version of the task. This suggests that an optimum level of glutamate receptor activity is important for memory formation. This hypothesis is supported through findings that both inhibition of glutamate receptor activity, or glutamate excess, can produce amnesia for the taste-avoidance task. For example, injections of monosodium glutamate produce amnesia for taste-avoidance learning (Gibbs and Ng, 1977; Patterson et al., 1986). Injections of glutamate agonists, such as 1-aminocyclopentane-1,3-dicarboxylic acid (ACPD) and 2-aminobicyclo [2.1.1]hexane-2.5-dicarboxylic acid-I (ABHxD-1), are also amnestic (Salinska and Stafiej, 2003). Lastly, injection of L-aspartic acid β-hydroxamate, which inhibits astrocytic removal of glutamate, also produces amnesia in this task (Gibbs et al., 2004).

We hypothesized that, under conditions of social isolation, increased corticosterone levels create increases in glutamate receptor activity that are amnestic for the one-trial taste-avoidance task. We evaluated this hypothesis by examining the effects of memantine on memory formation for taste-avoidance learning in day-old chicks intentionally exposed to social isolation stress. We predicted that memantine would improve memory formation that is typically impaired by social isolation.

2. Method

2.1. Subjects

Male, leghorn-derived chicks ($N = 534$, average weight = 30 g), purchased locally (Hyline International, Elizabethtown, PA), arrived one day after hatching. All chicks were housed together for 1 h to allow acclimation to the warm behavioral testing room (maintained on a 12 hour light/dark cycle, at 38.5–40.5 °C and 45–51% humidity). Pairs of chicks were then housed in opaque, Plexiglas pens (22.8 cm × 22.8 cm × 22.8 cm) that were open at the bottom and sat on white paper towels. One chick of each pair was marked on its back with a blue dye to facilitate identification. All experiments were in compliance with APA ethical standards of care and treatment of animals and were approved by the Dickinson College Animal Care and Use Committee.

2.2. Drugs

Memantine hydrochloride was purchased from Sigma Chemical Company (St. Louis, MO) and was prepared fresh daily by dissolving the drug in 0.9% sterile saline to the desired concentrations. All drugs were administered intraperitoneally at a volume of 0.1 mL using a 1.0 ml syringe fitted with a 27-gauge needle. Each chick received one injection, and chicks in the same pen were given the same drug treatment. Memantine was observed to produce behavioral side effects at doses greater than 15.0 mM, such as unresponsiveness to the bead at training. In each experiment, several sessions were conducted with a smaller number of animals (typically 50–80 chicks) in which all drug conditions were present.

2.3. Social isolation stress

Stress was applied in the form of 1 h of social isolation, in which the chicks were placed individually into the behavioral testing pens.

2.4. Procedure

A strong version of the taste-avoidance task was used; retention in control animals is generally high with strong training (Patterson et al., 1986). Thirty minutes before training, the chicks were injected with saline or one of several concentrations of memantine (see Fig. 1). Behavioral observers were blind to the injection condition (saline or memantine). Ten min following injection, chicks were pre-trained with a 30 s presentation of a 2 mm water-coated pearl bead (glued to the end of a thin wire). Pre-training encourages the chick to peck at training. Timing was started once each chick oriented toward the bead (moved its head toward the bead). The behavioral response (pecking behavior) toward the bead was recorded as "peck" or "no peck." Pre-training was repeated 10 min later. At 30 min post-injection, the chicks were trained by a 30 s presentation of a 3 mm chrome bead coated with 100% MeA. The pecking behavior of each chick was recorded as "peck," "peck with disgust," or "no peck." Peck with disgust is defined as beak-wiping or head-shaking following pecking of the bead. Chicks that did not peck or failed to show a disgust reaction at training were not used in the final analyses.

Avoidance training. Four hours after training, avoidance was tested by presentation of a dry 3 mm chrome bead to the chick for 30 s. The pecking behavior of each chick was recorded as "peck" or "avoid." Amnesia was defined as pecking at the bead during test, whereas retention was defined as avoidance of the bead at test. The data were analyzed using chi-square tests for independence.

Discrimination training. Twenty minutes after the first test trial, the chicks were presented with a novel, 3 mm white bead for 30 s. While

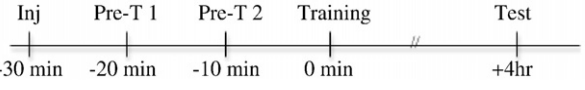

Fig. 1. Timeline of behavioral training and testing. Chicks were injected with saline or memantine 30 min before training. Ten min following injection, the chicks were pre-trained with a 30 s presentation of a 2 mm water-coated pearl bead. Pre-training was repeated 10 min later. At 30 min post-injection, the chicks were trained by a 30 s presentation of a 3 mm chrome bead coated with 100% MeA. Four hours after training, avoidance was tested by presentation of a dry 3 mm chrome bead to the chick for 30 s.

other researchers have used a shorter interval at test between the test and novel bead, Crowe and Hale (2002) reported that chicks tested with shorter intervals often displayed generalized avoidance of the test beads.

During the test trials, behavior was recorded as the number of pecks to each type of test bead. Chicks not pecking at the novel bead were not used in the final analysis. The behavior of the chick was then transformed into a discrimination ratio, in which the number of pecks of the white novel bead is divided by the number of pecks to the chrome bead plus the novel white bead. Amnesia is indicated by a discrimination ratio approaching 0.5 (pecking both beads). Learning is indicated by a discrimination ratio closer to 1.0 (in which the chick pecks the novel bead but not the aversive bead). These results were analyzed using a *t*-test.

2.4.1. Experiment 1: effects of memantine in control, non-stressed conditions

Chicks ($N=262$) were housed in pairs and received either an injection of saline (control) or one of several concentrations of memantine: 0.5 mM, 1.0 mM, 5.0 mM, 10.0 mM, or 15.0 mM. No social isolation was applied. Ten minutes later, pre-training began. The chicks were trained on the avoidance training method as described above.

2.4.2. Experiment 2: effects of memantine in chicks given 1 h pre-injection social isolation stress and trained using the avoidance training method

Chicks ($N=225$) were given social isolation for 1 h before injection. At the end of the social isolation period, the chicks received either an injection of saline (control) or one of several concentrations of memantine: 0.1 mM, 0.5 mM, 1.0 mM, 5.0 mM, 10.0 mM, or 15.0 mM. Immediately following injection, the chicks were returned to the pens in pairs. Ten minutes later, pre-training began. The chicks were trained on the avoidance training method as described above.

2.4.3. Experiment 3: effect of 5.0 mM memantine in chicks given 1 h pre-injection social isolation and trained using the discrimination training method

Gibbs, et al. (2008) argued that the avoidance method used in this task is less sophisticated than that of discrimination learning, in which chicks are tested with two different beads. General response inhibition can be ruled out with discrimination training, because chicks that do not peck the novel bead are not used in the final analysis. In addition, because the discrimination ratio calculated measures the ability of the chick to avoid the bead associated with training but peck the novel bead, this measure more clearly assesses memory formation for the association between the training bead and its consequences (bad taste). Finally, the discrimination method yields parametric data that can be analyzed by *t*-tests and ANOVA, more sensitive statistical analyses. We therefore examined if the effect of 5.0 mM memantine found in Experiment 2 could be reproduced using the discrimination training method.

Chicks ($N=47$) were given social isolation for 1 h before injection. Each pair received either an injection of saline (control) or 5.0 mM memantine as described for Experiment 2. Immediately following injection, the chicks were returned to the pens in pairs. Ten minutes later, pre-training began. The chicks were trained and tested using the discrimination training method as described above.

3. Results

3.1. Experiment 1: effects of memantine in control, non-stressed conditions

As Fig. 2 demonstrates, when chicks were not stressed by isolation and given strong training, 15.0 mM memantine significantly impaired memory formation (56% avoidance) compared to saline controls (83% avoidance; $\chi^2=9.38$; $p<.01$; $\Phi=0.30$). There were no significant effects of 0.5 mM, 1.0 mM, 5.0 mM, or 10.0 mM memantine.

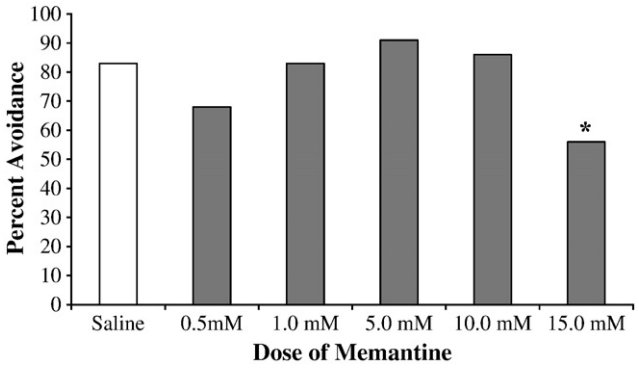

Fig. 2. Chicks ($N=262$) were housed in pairs and received either an injection of saline (control) or one of several concentrations of memantine: 0.5 mM, 1.0 mM, 5.0 mM, 10.0 mM, or 15.0 mM. The chicks were given strong training and no social isolation was applied. *, percent avoidance for 15.0 mM memantine chicks compared to control ($\chi^2=9.38$; $p<.01$; $\Phi=0.30$).

3.2. Experiment 2: effects of memantine in chicks given 1 h pre-injection social isolation and trained using the avoidance training method

Fig. 3 shows that, when chicks were stressed by pre-injection isolation and given strong training, both 1.0 mM and 5.0 mM memantine significantly enhanced memory formation (1.0 mM, 83% avoidance; 15.0 mM, 86% avoidance) compared to the saline controls (60% avoidance, $\chi^2=5.16$; $p<.05$; $\Phi=0.24$, saline vs. 1.0 mM memantine, and $\chi^2=6.68$; $p<.01$; $\Phi=0.27$, saline vs. 5.0 mM memantine). There were no significant effects of 0.1 mM, 0.5 mM, 10.0 mM, or 15.0 mM memantine. Percent avoidance in the control group in Experiment 2 was significantly less than percent avoidance seen in Experiment 1 controls ($\chi^2=4.55$; $p<.05$; $\Phi=0.20$).

3.3. Experiment 3: effects of memantine in chicks given 1 h pre-injection social isolation and trained using the discrimination training method

5.0 mM memantine again improved memory formation compared to saline-injected controls (t (47) $=2.29$; $p=0.027$; $d=0.31$; see

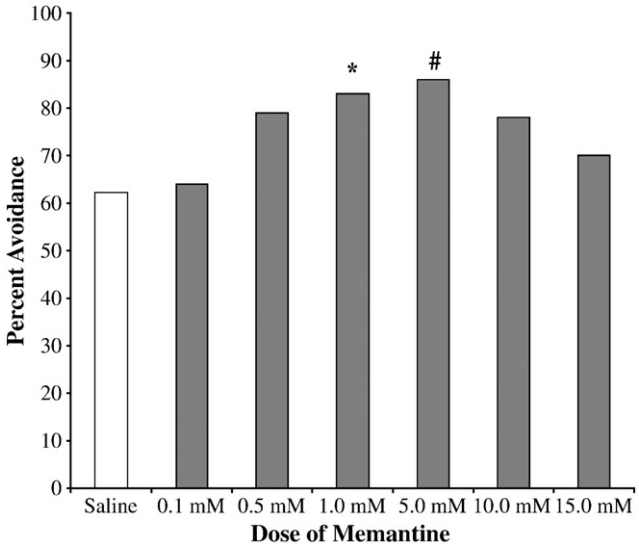

Fig. 3. Chicks ($N=225$) were housed singly for 1 h upon arrival. Immediately following injection, the chicks were returned to the pens in pairs. Each pair received either an injection of saline (control) or one of several concentrations of memantine: 0.1 mM, 0.5 mM, 1.0 mM, 5.0 mM, 10.0 mM, or 15.0 mM. *, percent avoidance for 1.0 mM memantine chicks compared to control ($\chi^2=5.16$; $p<.05$; $\Phi=0.24$). #, percent avoidance for 5.0 mM memantine chicks compared to control ($\chi^2=6.68$; $p<.01$; $\Phi=0.27$).

Fig. 4). Percent avoidance in these two groups was comparable to that seen in Experiment 2 (saline-injected controls, 52.0% avoidance; 5.0 mM memantine group, 79.2% avoidance; $\chi^2 = 3.99$, $p < 0.05$; $\Phi = 0.29$). There were no significant differences in the average number of pecks to the novel white bead in the saline-injected controls (8.3) compared to the memantine-injected group (10.1).

4. Discussion

The results of the present study indicate that under normal, non-stressed conditions, control animals show high levels of avoidance at test and memantine, like other NMDA receptor antagonists, impairs memory. However, when chicks are exposed to isolation stress during the pre-training injection period, memory formation for saline-injected control animals is impaired and memantine significantly improves memory in an inverted U-shaped dose response function.

In Experiment 1, chicks injected with saline showed high levels of avoidance, indicating that strong training occurred, whereas chicks injected with memantine (15.0 mM) exhibited significant amnesia. These results confirm previous findings that inhibition of NMDA receptor activation produces amnesia in chicks trained on the strong version of the one-trial taste-avoidance task (Burchuladze and Rose, 1992; Ng et al., 1997; Sherry and Crowe, 2008). Studies with other paradigms support the hypothesis that NMDA receptor activation is important in early memory formation. For example, visual imprinting alters NMDA receptor binding levels in day-old chicks (McCabe and Horn, 1988; Johnston et al., 1995), while disruption of NMDA activity impairs such imprinting (McCabe et al., 1992). Disruption of NMDA receptors also impairs auditory imprinting in the chick (Bock et al., 1996). In addition, NMDA receptor activity has been shown to be important for both spatial memory in black-capped chickadees (Shiflett et al., 2004) and song learning in the zebra finch (Ding and Perkel, 2004).

Studies suggest that activation of NMDA receptors is critical for the acquisition and formation of memory for the one-trial taste-avoidance task in day-old chicks, while non-NMDA receptor activation may play a role in later processes, such as the maintenance or consolidation of memories. Rickard et al. (1994) found that 6,7-dinitroquinoxaline-2,3-dione (DNQX), an antagonist of kainate and AMPA receptors, produced amnesia in the taste-avoidance task when administered 20 min after training. Injections of 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), another AMPA receptor antagonist, given 4 to 5 h post-training

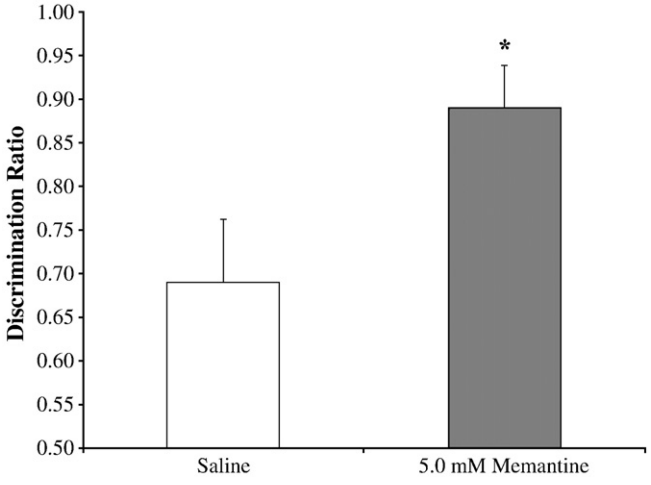

Fig. 4. Chicks ($N = 47$) were housed singly for 1 h upon arrival. Immediately following injection, the chicks were returned to the pens in pairs. Each pair received either an injection of saline (control) or 5.0 mM memantine. The chicks were trained on a discrimination version of the one-trial taste-avoidance task. *, discrimination ratio comparing 5.0 mM memantine group to control (t (47) = 2.29; $p = 0.027$; $d = 0.31$).

also produced amnesia, and training on the taste-avoidance task was associated with an increase in affinity for AMPA receptors measured 6 h after training (Steele and Stewart, 1995). However, Steele and Stewart found that CNQX administered either before training or 5 min after training had no effect. Burchuladze and Rose (1992) also reported that DNQX, CNQX and 6-nitro-7-sulphamoyl-benzoquinoxaline-2,3-dione (NBQX) did not produce amnesia when given 5 min after training.

In Experiment 2, chicks were housed singly for 1 h upon arrival and immediately following injection, the chicks were returned to the pens in pairs. The percent avoidance in saline-injected controls was significantly lower than percent avoidance in controls in Experiment 1 (60% compared to 83%), suggesting that social isolation produces significant amnesia in the strong version of the taste-avoidance task. Social isolation in chicks produces increased behavioral indicators of stress, such as distress calls, defecation, and escape behaviors (Jones and Merry, 1988). Social isolation also impairs key-pecking extinction (Zolman and Hall, 1977), delays extinction of imprinting (Rimpau and Schulman, 1981), and alters the timing of phases of memory formation (DeVaus et al., 1980).

Social isolation is associated with an increase in corticosterone for at least 15 min following separation (Feltenstein et al., 2003). It is possible that this rise in corticosterone alters levels of glutamate in the chick brain at the time of training. In the rat hippocampus, acute stress weakens high-frequency stimulation-induced LTP (which is dependent on NMDA receptor activation); this effect is dependent on activity of the glucocorticoid receptor (Foy et al., 1987; Yang et al., 2004). Acute treatment with corticosterone increases evoked glutamate release from hippocampal synaptosomes; this effect is blocked by the glucocorticoid receptor blocker mifepristone (Wang and Wang, 2009). Future studies should examine the effects of social isolation and corticosterone on glutamate release and post-synaptic NMDA receptor activity at the time of training in the taste-avoidance task.

In Experiment 2, 1.0 mM and 5.0 mM memantine improved memory formation in chicks given social isolation before training. These results support the hypothesis that memantine, while normally amnestic, can ameliorate memory impairment by decreasing excess post-synaptic NMDA receptor activity. Memantine has been shown to decrease memory impairment found in AD (Emre et al., 2008; McKeage, 2009). Pre-treatment with memantine also prevented both spatial and non-spatial memory loss produced by 3,4-methylenedioxymethamphetamine (MDMA) in the Morris water maze (Camarasa et al., 2008). In honeybees, memantine facilitated olfactory conditioning and ameliorated memory impairment produced by the glutamate transporter inhibitor L-trans-2,4-pyrrolidine dicarboxylate (Si et al., 2004). Parsons and his colleagues (see Parsons et al., 1993, 1995, 1996) have demonstrated that, due to a strong functional voltage dependency and fast offset kinetics, memantine can exit the NMDA channel under conditions of normal physiological activation by glutamate, but also block any sustained high levels of glutamate in pathological conditions, as might be found in moderate AD or the conditions of training found in the current study.

Because improved memory in this task is defined by an inhibition of response (avoiding the bead at test), it is possible that the results in Experiment 2 are due to non-specific effects of memantine. Creeley et al. (2006) have argued that memantine is only capable of ameliorating memory impairments at doses that produce locomotor side effects. This is unlikely in the present experiment because (1) in Creeley et al., memantine increased locomotor behavior, which here might lead to more pecking rather than less pecking, (2) memantine at doses higher than 5.0 mM were associated with poor retention, which is defined as increased levels of pecking rather than avoidance (if memantine impaired general behavior, such as pecking, one would expect to find decreased pecking as the dose of memantine increased), and (3) the results of Experiment 3 demonstrate that memantine also produces reliable memory enhancement using a discrimination learning task.

Previous results have shown that, in the chick one-trial taste-avoidance task, weak training can be enhanced with either corticosterone (Sandi and Rose, 1994) or social isolation (Johnston and Rose, 1998). With strong training, injection of corticosterone (Sandi and Rose, 1997) produces significant amnesia. The current results complement these findings and show that social isolation also produces significant amnesia for strong training (Experiments 1 and 2 control animals). In addition, the present results indicate that that the NMDA receptor antagonist memantine impairs memory for strong training but improves memory under conditions of social isolation. Future studies should examine the effects of memantine under weak training conditions, accompanied by injections of corticosterone or social isolation. By further reducing post-synaptic NMDA receptor activity, memantine would most likely produce amnesia for weak training. As has been shown with MK801 administration, memantine is also most likely to inhibit the facilitating effect of corticosterone on memory formation for weak training (Venero and Sandi, 1997). With strong training, memantine might ameliorate the amnestic effects of corticosterone, as we have shown here that it ameliorates social isolation-induced amnesia.

The mechanism by which memantine might ameliorate isolation stress-induced impairment of memory formation is not fully understood. Clearly, reducing glutamate receptor activity under conditions in which excess glutamate receptor activity might occur (such as social isolation) would result in more normal levels of NMDA receptor activation. Memantine is uniquely qualified to quickly work in this way. The current results extend the findings that memantine can ameliorate memory impairment and supports the hypothesis, as suggested by Parsons et al. (2007), that memantine, under conditions of amnestic glutamate receptor activity, can facilitate normalized memory acquisition.

References

Abrahám I, Juhász G, Kékesi KA, Kovács KJ. Effect of intrahippocampal dexamethasone on the levels of amino acid transmitters and neuronal excitability. Brain Res 1996;733:56–63.

Bermant G. Intensity and rate of distress calling in chicks as a function of social contact. Anim Behav 1963;11:514–7.

Bock J, Wolf A, Braun K. Influence of the N-methyl-D-aspartate receptor antagonist DL-2-amino-5-phosphonovaleric acid on auditory filial imprinting in the domestic chick. Neurobiol Learn Mem 1996;65:177–88.

Burchuladze R, Rose SPR. Memory formation in day old chicks requires NMDA but not non-NMDA glutamate receptors. Eur J NeuroSci 1992;4:533–8.

Butelman ER. A novel NMDA antagonist MK801 impairs performance in a hippocampal dependent spatial learning task. Pharmacol Biochem Behav 1989;34:13–6.

Camarasa J, Marimon JM, Rodrigo T, Escubedo E, Pubill D. Memantine prevents the cognitive impairment induced by 3, 4-methylenedioxymethamphetamine in rats. Eur J Pharmacol 2008;589:132–9.

Chen HS, Lipton SA. The chemical biology of clinically tolerated NMDA receptor antagonists. J Neurochem 2006;97:1611–26.

Creeley C, Wozniak DF, Labruyere J, Taylor GT, Olney JW. Low doses of memantine disrupt memory in adult rats. J Neurosci 2006;26:3923–32.

Crowe SF, Hale MW. Carryover effects associated with the single-trial passive avoidance learning task in the young chick. Neurobiol Learn Mem 2002;75:321–31.

Daisley JN, Rose SP. Amino acid release from the intermediate medial hyperstriatum ventrale IMHV; of day-old chicks following a one-trial passive avoidance task. Neurobiol Learn Mem 2002;77:185–201.

DeVaus JE, Gibbs ME, Ng KT. Effects of social isolation on memory formation. Behav Neural Biol 1980;29:473–80.

Ding L, Perkel DJ. Long-term potentiation in an avian basal ganglia nucleus essential for vocal learning. J Neurosci 2004;24:488–94.

Doody RS, Tarot PN, Pfeiffer E, Olin JT, Graham SM. Meta-analysis of six-month memantine trials in Alzheimer's disease. Alzheimers Demen 2007;3:7-17.

Emre M, Mecocci P, Stender K. Pooled analyses on cognitive effects of memantine in patients with moderate to severe Alzheimer's disease. J Alzheimer's Dis 2008;14:193–9.

Feltenstein MW, Lambkin LC, Webb HE, Warnock JE, Khan SI, Khan IA, et al. Corticosterone response in the chick separation-stress paradigm. Physiol Behav 2003;78:489–93.

Foy MR, Stanton ME, Levine S, Thompson RF. Behavioral stress impairs long-term potentiation in rodent hippocampus. Behav Neural Biol 1987;48:138–49.

Gibbs ME, Ng KT. Psychobiology of memory: towards a model of memory formation. Biobehav Rev 1977;1:113–36.

Gibbs ME, Hertz L, Ng KT. Inhibition of short-term memory formation in the chick by blockade of extracellular glutamate uptake. Neurobiol Learn Mem 2004;81:115–9.

Gibbs ME, Johnston AN, Mileusnic R, Crowe SF. A comparison of protocols for passive and discriminative avoidance learning tasks in the domestic chick. Brain Res Bull 2008;76:198–207.

Johnston AN, Rose SP. Isolation-stress-induced facilitation of passive avoidance memory in the day-old chick. Behav Neurosci 1998;112:929–36.

Johnston AN, Rogers LJ, Dodd PR. [3H]MK-801 binding asymmetry in the IMHV region of dark-reared chicks is reversed by imprinting. Brain Res Bull 1995;37:5–8.

Jones RB, Merry BJ. 1988; Individual or paired exposure of domestic chicks to an open field: some behavioural and adrenocortical consequences. Behav Process 1995; 16: 75–86.

Liu L, Wang C, Ni X, Sun J. A rapid inhibition of NMDA receptor current by corticosterone in cultured hippocampal neurons. Neurosci Lett 2007;420:245–50.

Lowy MT, Gaul L, Yamamoto B. Adrenalectomy attenuates stress-induced elevations in extracellular glutamate concentrations in the hippocampus. J Neurochem 1993;61: 1957–60.

Lynch MA. Long-term potentiation and memory. Physiol Rev 2004;84:87-136.

McCabe BJ, Horn G. Learning and memory: regional changes in N-methyl-D-aspartate receptors in the chick brain after imprinting. Proc Natl Acad Sci USA 1988;85: 2849–53.

McCabe BJ, Davey JE, Horn G. Impairment of learning by localized injection of an N-methyl-D-aspartate receptor antagonist into the hyperstriatum ventrale of the domestic chick. Behav Neurosci 1992;106:947–53.

McKeage K. Memantine: a review of its use in moderate to severe Alzheimer's disease. CNS Drugs 2009;23:881–97.

Misztal M, Danysz W. Comparison of glutamate antagonists in continuous multiple-trial and single-trial dark avoidance. Behav Pharmacol 1995;6:550–61.

Mitsacos A, Dermon CR, Stassi K, Kouvelas ED. Localization of L-glutamate binding sites in chick brain by quantitative autoradiography. Brain Res 1990;513:348–52.

Moghaddam B, Bolinao ML, Stein-Behrens B, Sapolsky R. Glucocorticoids mediate the stress-induced extracellular accumulation of glutamate. Brain Res 1994;655:251–4.

Morris RGM, Anderson E, Lynch GS, Baudry M. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartame agonist, AP5. Nature 1986;319:774–6.

Ng KT, O'Dowd BS, Rickard NS, Robinson SR, Gibbs ME, Rainey C, et al. Complex roles of glutamate in the Gibbs–Ng model of one-trial aversive learning in the new-born chick. Neurosci Biobehav Rev 1997;21:45–54.

Parsons CG, Gruner R, Rozental J, Millar J, Lodge D. Patch clamp studies on the kinetics and selectivity of N-methyl-D-aspartate receptor antagonism by memantine 1-amino-3,5-dimethyladamantan. Neuropharmacology 1993;32:1337–50.

Parsons CG, Quack G, Bresink I, Baran L, Przegalinski E, Kostowski W, et al. Comparison of the potency, kinetics and voltage-dependency of a series of uncompetitive NMDA receptor antagonists in vitro with anticonvulsive and motor impairment activity in vivo. Neuropharmacology 1995;34:1239–58.

Parsons CG, Panchenko VA, Pinchenko VO, Tsyndrenko AY, Krishtal OA. Comparative patch-clamp studies with freshly dissociated rat hippocampal and striatal neurons on the NMDA receptor antagonistic effects of amantadine and memantine. Eur J NeuroSci 1996;8:446–54.

Parsons CG, Stöffler A, Danysz W. Memantine: a NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system — too little activation is bad, too much is even worse. Neuropharmacology 2007;53:699–723.

Patterson TA, Rose SPR. Memory in the chick: multiple cues, distinct brain locations. Behav Neurosci 1992;106:465–70.

Patterson TA, Alvarado MC, Warner IT, Bennett EL, Rosenzweig MR. Memory stages and brain asymmetry in chick learning. Behav Neurosci 1986;100:856–65.

Patterson TA, Gilbert DB, Rose SPR. Pre- and post-training lesions of the intermediate medial hyperstriatum ventrale and passive avoidance learning in the chick. Exp Brain Res 1990;80:189–95.

Rajecki DW, Soumi SJ, Scott EA, Campbell B. Effects of social isolation and social separation in domestic chicks. Dev Psychol 1977;13:143–55.

Rickard NS, Poot AC, Gibbs ME, Ng KT. Both non-NMDA and NMDA glutamate receptors are necessary for memory consolidation in the day-old chick. Behav Neural Biol 1994;62:33–40.

Rimpau JB, Schulman AH. A comparison of the effects of social rearing and social training on approach responding of Gallus chicks. Behav Processes 1981;6:37–46.

Robbins TW, Murphy ER. Behavioural pharmacology: 40+ years of progress, with a focus on glutamate receptors and cognition. Trends Pharmacol Sci 2006;27:141–8.

Roberts M, Shapiro M. NMDA receptor antagonists impair memory for nonspatial, socially transmitted food preference. Behav Neurosci 2002;116:1059–69.

Rose SPR. God's organism? The chick as a model system for memory studies. Learn Mem 2000;7:1-17.

Rose SPR. Memory beyond the synapse. Neuron Glia Biology 2004;1:211–7.

Salinska E, Stafiej A. Metabotropic glutamate receptors mGluRs; are involved in early phase of memory formation: possible role of modulation of glutamate release. Neurochem Int 2003;435:469–74.

Salinska EJ, Chaudhury D, Bourne RC, Rose SPR. Passive avoidance training results in increased responsiveness of voltage- and ligand-gated calcium channels in chick brain synaptoneurosomes. Neuroscience 1999;7:1507–14.

Sandi C, Rose SPR. Corticosterone enhances long-term retention in one day old chicks trained in a weak passive avoidance learning paradigm. Brain Res 1994;647:106–12.

Sandi C, Rose SP. Training-dependent biphasic effects of corticosterone in memory formation for a passive avoidance task in chicks. Psychopharmacology 1997;133: 152–60.

Sandi C, Rose SPR, Patterson TA. Unilateral hippocampal lesions prevent recall of a passive avoidance task in day-old chicks. Neurosci Lett 1992;141:255–81.

Sanger DJ. NMDA antagonists disrupt timing behavior in rats. Behav Pharmacol 1992;3: 593–600.

Sato S, Osanai H, Momma T, Harada T, Hirano A, Saito M, et al. Acute effect of corticosterone on N-methyl-D-aspartame receptor-mediated Ca2+ elevation in mouse hippocampal slices. Biochem Biopsys Res Commun 2004;321:510–3.
Sherry JM, Crowe SF. Inhibition of cyclin-dependent kinase 5 by roscovitine impairs memory consolidation and reconsolidation in the day-old chick. Pharmacol Biochem Behav 2008;91:59–66.
Shiflett MW, Tomaszycki ML, Rankin AZ, DeVoogd TJ. Long-term memory for spatial locations in a food-storing bird *Poecile atricapilla*; requires activation of NMDA receptors in the hippocampal formation during learning. Behav Neurosci 2004;118: 121–30.
Si A, Helliwell P, Maleszka R. Effects of NMDA receptor antagonists on olfactory learning and memory in the honeybee *Apis mellifera*. Pharmacol Biochem Behav 2004;77: 191–7.
Steele RJ, Stewart MG. Involvement of AMPA receptors in maintenance of memory for a passive avoidance task in day-old domestic chicks *Gallus domesticus*. Eur J NeuroSci 1995;7:1297–304.
Steele RJ, Stewart MG, Rose SPR. Increases in NMDA receptor binding are specifically related to memory formation for a passive avoidance task in the chick: a quantitative autoradiographic study. Brain Res 1995;674:352–6.
Stewart MG, Bourne RC, Steele RJ. Quantitative autoradiographic demonstration of changes in binding to NMDA-sensitive [3H]glutamate and [3H]MK801, but not [3H] AMPA receptors in chick forebrain 30 minutes after passive avoidance training. Eur J NeuroSci 1992;4:936–43.
Ungerer A, Mathis C, Mélan C, De Barry J. The NMDA receptor antagonists, CPP and gamma-L-glutamyl-L-aspartate, selectively block post-training improvement of performance in a Y-maze avoidance learning task. Brain Res 1991;549:59–65.
Venero C, Sandi C. Effects of NMDA and AMPA receptor antagonists on corticosterone facilitation of long-term memory in the chick. Eur J NeuroSci 1997;9:1923–8.
Wang CC, Wang SJ. Modulation of presynaptic glucocorticoid receptors on glutamate release from rat hippocampal nerve terminals. Synapse 2009;63:745–51.
Watson DJ, Stanton ME. Intrahippocampal administration of an NMDA-receptor antagonist impairs spatial discrimination reversal learning in weanling rats. Neurobiol Learn Mem 2009;92:89–98.
Xu X. NMDA receptor antagonist MK-801 selectively impairs learning of the contiguity of the conditioned stimulus and unconditioned stimulus in goldfish. Pharmacol Biochem Behav 1997;58:491–6.
Yang CH, Huang CC, Hsu KS. Behavioral stress modifies hippocampal synaptic plasticity through corticosterone-induced sustained extracellular signal-regulated kinase/ mitogen-activated protein kinase activation. J Neurosci 2004;24:11,029–34.
Zajaczkowski W, Frankiewicz T, Parsons CG, Danysz W. Uncompetitive NMDA receptor antagonists attenuate NMDA-induced impairment of passive avoidance learning and LTP. Neuropharmacology 1997;36:961–71.
Zolman JF, Hall JA. Effects of isolation rearing on keypecking in young domestic chicks. Bull Psychon Soc 1977;10:506–8.