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Memantine facilitates memory consolidation and reconsolidation in the day-old chick

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ABSTRACT

Memantine is a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist that has been approved for the treatment of the cognitive deficits noted in Alzheimer's disease. While there is a body of research that supports memantine's facilitative action upon memory compromise, this series of studies aimed to investigate the effects of this drug in healthy animals with intact memory functioning. A 0.1 mM dose of memantine injected immediately after a weakly aversive training event (i.e. 20% v/v methyl anthranilate) was found to enhance passive avoidance learning for this event in day-old chicks up to 24 h following training. The same dose of memantine was also observed to enhance memory for the training event when it was administered in conjunction with a reminder trial. These results suggest that memantine is capable of facilitating both memory consolidation as well as memory reconsolidation. It was concluded that memantine's mechanism may involve the short-term or intermediate memory phases of the Gibbs and Ng model of memory, and that the current findings represent enhancement of intact memory, rather than amelioration of memory compromise.

1. Introduction

Memantine is a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist currently approved for the treatment of Alzheimer's disease (AD) in the United States and Europe. In human clinical trials, memantine has been noted to improve cognition in AD as well as in vascular dementia (2002; Peskind et al., 2006; Winblad, Jones, Wirth, Stöffler, & Möbius, 2007; Winblad & Poritis, 1999). Memantine has also been demonstrated to enhance spatial memory in aged rats (Beracochea, Boucard, Trocme-Thibierge, & Morain, 2008). Recently, Barber and colleagues, using the day-old chick, have demonstrated that the drug can facilitate memory that has been compromised by isolation-induced stress (Barber, Meyers, & McGettigan, 2010).

While the major target of memantine's therapeutic mechanism is the NMDA receptor, memantine may also act as an antagonist at serotonin (5-HT) and nicotinic acetylcholine (ACh) receptors (see Rammes, Danysz, and Parsons (2008), Rogawski and Wenk (2003), for reviews). In contrast, Drever et al. (2007) have demonstrated that memantine's enhancement of synaptic transmission in the mouse hippocampus is ameliorated by application of the muscarinic ACh receptor antagonist scopolamine, and that memantine reverses the inhibitory effects of scopolamine on learning and memory. Barber and Haggarty (2010) have also shown facilitation of scopolamine-compromised memory by memantine in the day-old chick. These findings support the contention that cholinergic pathways, in addition to glutamatergic pathways, may be involved in memantine's effect on memory.

It should be noted that memantine's antagonistic effect on NMDA receptors in addition to its facilitatory effect on memory, poses something of a paradox, as activation of NMDA receptors has been widely demonstrated to be involved in memory function (e.g. Morris, Anderson, Lynch, & Baudry, 1986; Whitlock, Heynen, Shuler, & Bear, 2006). An explanation for this seemingly contradictory mechanism has been discussed in a review by Parsons, Stöffler, and Danysz (2007). These investigators have suggested that memantine's facilitation of long-term potentiation (LTP) and of memory occurs in a dose-dependent manner via restoring glutamatergic homeostasis. The authors further contend that the over-stimulation of NMDA receptors is just as detrimental to memory function as is complete or near-complete blockade, and that memantine may help to ameliorate the inhibitory effect caused by over-stimulation.

The effect of memantine on unimpaired subjects has also been investigated; however, the findings have been less conclusive than those noted in studies of memory-compromised subjects. A recent review has suggested that memantine either has no effect or results in impairment of memory in healthy subjects (Repantis, Laisney, &

Abbreviations: PAL, passive avoidance learning; MeA, methyl anthranilate.

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Heuser, 2010). Similarly, in some animal studies, various doses of memantine have been shown to either have no effect or to impair memory in rats (Réus et al., 2008) and day-old chicks (Barber et al., 2010). In contrast, other research using healthy rats has noted a facilitatory effect of memantine on memory functioning (Wise & Lichtman, 2007; Zoladz et al., 2006) and improved maintenance of hippocampal LTP *in vivo* (Barnes, Danysz, & Parsons, 1996). The effect of memantine on intact memory thus continues to be a topic of contention.

Another issue of relevance in the contemporary study of memory is the effect of memantine on the process of reconsolidation. Reconsolidation refers to the process that takes place once a previously-consolidated memory is retrieved from storage and once again becomes transformed into a labile and modifiable state. The reactivated trace is then consolidated once more, or *reconsolidated* in a state that includes the additional information acquired at the time of reactivation (for a review, see Tronson & Taylor, 2007). To date, only few studies have investigated memantine's effect on the process of reconsolidation, and in general, this evidence has indicated an inhibitory effect. Popik, Wrobel, and Bisaga (2006) found that memantine, when injected at the time of a retrieval phase (i.e. at the time when the memory is recalled and made labile), prevented morphine-primed reinstatement of morphine-conditioned place preference in rats. This suggests that memantine interfered with reconsolidation such that the memory of place preference in the rats was not able to be recalled later at the time of testing, even when primed by the injection of morphine.

The aim of this series of studies was to investigate memantine's function in healthy day-old chicks, using both a weak and a strong aversive training experience and employing both consolidation and reconsolidation trials, in the context of a well studied training paradigm. The weak passive avoidance learning (PAL) task was employed in combination with the day-old chick, a paradigm that has been extensively studied (e.g. Crowe & Hale, 2002). To date, no published study has examined the effect of memantine on the weak PAL task. The specific aims of the research were as follows: to determine the most effective dose of memantine necessary to enhance memory using a weak training experience (Experiment 1); to determine the time window over which injection of memantine was effective (Experiment 2); to investigate the length of time over which memantine had its facilitatory effect (Experiment 3), and; to investigate the ability of memantine to enhance memory reconsolidation (Experiment 4).

2. Method

2.1. Subjects

One-thousand one-hundred and sixty male day-old New Hampshire × White Leghorn chicks (*Gallus domesticus*; average weight of 45 g) were employed as subjects in the experiments: 240 each in Experiments 1 and 4, 360 in Experiment 2, and 320 in Experiment 3. The chicks were housed in wooden boxes (20 × 25 × 20 cm) with open tops and were kept in pairs so as to reduce any distress brought about by social isolation. The chicks were kept warm by a 60 W incandescent light bulb positioned above each box, and chick mash was provided *ad libitum*. For the purpose of identification during data collection, one chick in each pair was marked on the head with a black felt tip pen. Chicks were left alone to settle for at least 30 min prior to experimentation. Each experimental condition initially consisted of a group of 20 chicks, but depending on the number of chicks that successfully completed the baseline and training phases, the final number varied. Approximately 20% of chicks were excluded from analysis on the basis of failure to peck at the bead during the baseline and training phases.

2.2. Materials

Memantine (3,5-dimethyladamantan-1-amine) hydrochloride was injected subcutaneously in a volume of 0.1 mL per chick in all four experiments, using a 1 mL syringe with a 27 gauge needle. In Experiment 1, doses used were 0.1, 0.5, 1, 2 and 3 mM of memantine, and in Experiments 2–4, a dose of 0.1 mM was employed. Saline solution was injected in the control conditions. The PAL task required a chrome bead and two red glass beads (each fixed to the end of a wire rod) and the aversive substance methyl anthranilate (MeA). Where MeA was used at a concentration of 20% v/v, the MeA was diluted in ethanol. The number of pecks for each chick in each condition was recorded using a handset connected to a PC in the laboratory so that button presses on the handset could be recorded and summed automatically.

2.3. Procedure and design

All four experiments employed the PAL task, first introduced by Cherkin (1969), which exploits the chick's natural inclination to peck at novel objects. The aim of the task is to train chicks to avoid pecking at a target bead. The phases of the task are as follows: pretraining, in which chicks are presented twice with a water-coated chrome bead to encourage a pecking response; baseline, in which a water-coated red bead is presented and pecks recorded as a baseline measure; training, in which a second red bead coated with the aversive substance methyl anthranilate (MeA) is presented to the chicks; reminder (Experiment 4 only), in which chicks are shown a dry red bead but are not allowed to peck, in order to elicit recall for the training event; and test, in which chicks are exposed to a dry red bead as a measure of retention of the training. Refer to Fig. 1 for an outline of the timing of the phases in each of the four experiments, and see Crowe and Hale (2004) for further details on the PAL procedure. All phases involved a 10-s exposure to the bead only. Chicks that did not peck at either the baseline or training phases were excluded from the subsequent analysis.

All independent variables (IVs) were categorical in nature. In Experiment 1, the IVs were concentration of MeA at training and dose of memantine. In Experiment 2, the IVs were time of injection relative to the training phase and drug injected (saline vs. memantine). In Experiment 3, the IVs were time of test after the training phase and drug injected. In Experiment 4, the IVs were time of reminder trial after the training phase and injected drug. In all experiments, the dependent variable was a binary measure with the two levels coded as avoidance (i.e. no pecks to the red test bead, demonstrating memory for the training event) or no avoidance (i.e. one or more pecks to the red test bead, demonstrating a lack of memory for the training event). While previous studies using the PAL task have employed a number of dependent variables (see Crowe & Hamalainen, 2001; Gibbs, Johnston, Mileusnic, & Crowe, 2008), the binary measure described here was employed due to significant skew of the originally calculated continuous measure (an avoidance ratio; e.g. Crowe & Hale, 2004).

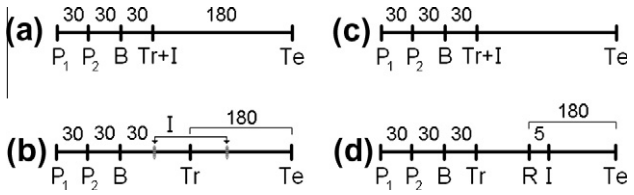

Fig. 1. Timeline of events for (a) Experiment 1 (dose response), (b) Experiment 2 (time of injection), (c) Experiment 3 (time of test) and (d) Experiment 4 (time of reminder trial). Numbers above the lines indicate minutes between events marked on the lines. P = pretraining, B = baseline, Tr = training, I = injection, R = reminder, Te = test.