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ScienceDirect
Neurobiology of Learning and Memory 88 (2007) 19–32
Neurobiology of Learning and Memory
www.elsevier.com/locate/ynlme

Cholinergic lesions produce task-selective effects on delayed matching to position and configural association learning related to response pattern and strategy

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Received 16 January 2007; revised 10 March 2007; accepted 13 March 2007
Available online 20 April 2007

Abstract

192IgG-saporin (SAP) was used to selectively destroy cholinergic neurons in the rostral basal forebrain (e.g., medial septum (MS) and vertical limb of the diagonal band of Broca (VDB)) and/or the caudal basal forebrain (e.g., nucleus basalis magnocellularis (NBM)) of ovariectomized Sprague–Dawley rats. The effects of these lesions on two different cognitive tasks, a delayed matching to position (DMP) T-maze task, and a configural association (CA) operant conditioning task, were evaluated and compared. Injecting SAP into either the MS or NBM significantly impaired acquisition of the DMP task. Analysis showed that the effects were due largely to an affect on response patterns adopted by the rats during training, as opposed to an effect on working memory performance. Notably, the impairment in DMP acquisition did not correlate with the degree of cholinergic denervation of the hippocampus. Despite the deficit, most animals eventually learned the task and reached criterion; however by the end of training, controls and animals that received SAP into either the MS or NBM appeared more likely to use an allocentric place strategy to solve the task, whereas animals that received SAP into both the MS and NBM were more likely to use an egocentric response strategy. Cholinergic lesions also produced a small but significant affect on acquisition of the CA task, but only with respect to response time, and only in the SAP-NBM-treated animals. SAP-NBM lesions also produced small but significant impairments in both the number of responses and response time during the acquisition of simple associations, possibly reflecting an effect on alertness or attention. Notably, the effects on CA acquisition were small, and like the effects on DMP acquisition did not correlate with the degree of cholinergic denervation of the hippocampus. We conclude that selective basal forebrain cholinergic lesions produce learning deficits that are task specific, and that cholinergic denervation of either the frontal cortex or hippocampus can affect response patterns and strategy in ways that affect learning, without necessarily reflecting deficits in working memory performance.

Keywords: 192IgG-saporin; T-maze; Operant conditioning; Learning; Choline acetyltransferase

1. Introduction

Cholinergic projections from the basal forebrain to the hippocampus and frontal cortex play an important role in cognitive processes; however, the degree to which damage to specific cholinergic projections contributes to deficits within specific cognitive domains is less clear. In particular, it is often not clear the extent to which damage to one set of cholinergic projections produces deficits that are limited to a particular cognitive domain, or the extent to which deficits on a particular task reflect the selective loss of a particular set of cholinergic projections. This is due, in part, to the fact that different laboratories produce lesions in different ways, individual studies often lesion only one subset of basal forebrain cholinergic projections rather than comparing lesions of different subsets, and studies often test performance using only one cognitive task. This makes it difficult to compare the degree of

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doi:10.1016/j.nlm.2007.03.007

impairment produced by different lesions across multiple cognitive domains.

In the present study, we compared the effects of selectively destroying cholinergic neurons in the rostral basal forebrain [e.g., medial septum (MS) and vertical limb of the diagonal band of Broca (VDB)] and in the caudal basal forebrain [e.g., nucleus basalis magnocellularis (NBM)] on acquisition of two different tasks, a delayed matching to position (DMP) T-maze task, and a configural association (CA) operant conditioning task, by the same set of animals. In addition, we chose to conduct these studies using ovariectomized female rats, rather than male rats which is more common. Ovariectomized female rats were used because (a) less is known about the effects of cholinergic lesions on cognitive performance in females than in males, (b) previous studies have demonstrated significant effects of cholinergic lesions on DMP acquisition in ovariectomized female rats (Gibbs, 2002), (c) studies have shown that estradiol replacement affects DMP acquisition in ovariectomized rats (Gibbs, 1999, 2000), and (d) some evidence suggests that loss of ovarian function may, over time, contribute to decreased basal forebrain cholinergic function as well as risk for age-related cognitive decline in postmenopausal women (Gibbs & Gabor, 2003). Since estradiol affects DMP acquisition in female rats, ovariectomized rats were used to avoid the confound of estradiol levels which vary across the estrous cycle.

Cholinergic neurons in the MS/VDB project primarily to allocortical fields and provide the primary cholinergic input to the hippocampus (Woolf, 1991), which is well known to play an important role in spatial learning and memory processes (Eichenbaum, 2006; Smith & Mizumori, 2006; Zola-Morgan & Squire, 1993). In addition, muscarinic receptor activation in the hippocampus and cortex have been shown to play an important role in memory consolidation (Power, Vazdarjanova, & McGaugh, 2003). Note that we have previously shown that cholinergic lesions in the MS/VDB impair acquisition of the DMP task in both males and females (Gibbs, 2002; Johnson, Zambon, & Gibbs, 2002), and have hypothesized that this is due specifically to the loss of hippocampal cholinergic inputs. In contrast, cholinergic neurons in the NBM project primarily to isocortical fields including frontal and prefrontal cortices (Woolf, 1991), which are known to be involved in directed attention, working memory, cognitive set switching, behavioral monitoring, and tasks requiring the ability to inhibit inappropriate responses (Collette, Hogge, Salmon, & Van der Linden, 2006; Dalley, Cardinal, & Robbins, 2004; Miller & Cummings, 1999).

Based on the anatomy of the cholinergic system, we predicted that acquisition of the DMP task would be impaired by MS/VDB (but not NBM) cholinergic lesions and that the severity of impairment would correlate specifically with the degree of cholinergic deafferentation of the hippocampus. While early studies suggested that the hippocampus also plays an essential role in configural learning (Rudy & Sutherland, 1989), subsequent studies showed that the critical neural system for configural associations is in the cortex with hippocampal outputs providing an important modulatory function (Rudy & Sutherland, 1995). Therefore, we predicted that acquisition of the CA task would be significantly affected by NBM cholinergic lesions, and that the severity of impairment would correlate with cholinergic deafferentation of the frontal cortex. Notably, the results generated a different picture, in which cortical projections from both the rostral and caudal cholinergic cell groups affected DMP acquisition, but had less effect on CA acquisition. In addition, the effects on DMP acquisition showed little correlation with cholinergic innervation of the hippocampus, and was more consistently correlated with cholinergic innervation of the frontal cortex. Analysis of the response patterns during acquisition of the DMP task suggest that the effects of the cholinergic lesions on DMP acquisition were due primarily to effects on response patterns and strategy selection rather than on interference with working memory processes. The results are consistent with several recent reports relating cholinergic activity to spatial learning, and provide novel insights about the effects of selective cholinergic lesions on these tasks.

2. Methods

2.1. Animals

Eighty-nine adult (300–325 g) ovariectomized Sprague–Dawley rats were purchased from Hilltop Laboratories and housed individually. All procedures were carried out in accordance with PHS policies and with the approval of the University of Pittsburgh's Institutional Animal Care and Use Committee.

2.2. Cholinergic lesions

192IgG-saporin (SAP; Advanced Targeting Systems, Inc., lot 24-87) was used to selectively destroy cholinergic neurons in the MS/VDB, and NBM. SAP was injected at a rate of 12 μL/h into either (a) the MS (MS; +0.5 mm from Bregma, 0.0.lateral, −5.6 mm from dura; 0.2 or 0.24 μg in 1.0 μL; $n = 19$), (b) bilaterally into the NBM (−2.4 mm from Bregma, 2.3 mm lateral, −7.0 mm from dura; 0.11 or 0.20 μg in 1.5 μL/side; $n = 23$), or (c) into both the MS and NBM ($n = 12$). Note that the doses of SAP were varied between animals in order to create variability in the degree of cholinergic cell loss, which is necessary for a correlational analysis. Controls received injections of normal saline into either the MS (1.0 μL, $n = 11$), bilaterally into the NBM (1.5 μL/side, $n = 16$) or into both the MS and NBM ($n = 8$). These parameters were derived from both prior and pilot studies showing that low doses of SAP injected directly into the MS/VDB or NBM selectively destroys cholinergic neurons in these regions without destroying nearby non-cholinergic cells (Baxter, Bucci, Gorman, Wiley, & Gallagher, 1995; Dornan et al., 1996; Johnson et al., 2002; Schliebs, Rossner, & Bigl, 1996).

2.3. DMP training and testing

After at least 2 weeks recovery, animals were handled daily, food restricted to 85% body weight, and then trained on the DMP task exactly as previously described (Gibbs, 1999). The T-maze consisted of an approach alley (4″ wide × 14″ long) and two goal arms (4″ wide × 12″ long). The walls of the maze were 5″ high and were constructed of black plexiglass. The top of the maze was constructed of clear plexiglass that allowed the animals to view the surrounding room, and was attached to