Inactivation of Hippocampus or Caudate Nucleus with Lidocaine Differentially Affects Expression of Place and Response Learning

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INTRODUCTION

Throughout the history of research on animal learning there have been conflicting views concerning the fundamental issue of what animals learn. Cognitive theorists such as Tolman (1932; 1948) proposed that animals acquire knowledge of "what-leads-to-what" that result in expectations of the consequences of their behavior. In contrast, following the pioneering work of Thorndike (1898; 1933) and Pavlov (1927), other theorists proposed that animal learning consists of the formation of stimulus-response (S-R) habits (Hull, 1943; Guthrie, 1935) or, simply, the learning of motor responses.

In experiments addressing this issue, rats were trained in mazes and subsequently tested in a variety of ways in an attempt to discover whether the learning was based on acquisition of knowledge or learning of responses (e.g., Tolman, Ritchie, & Kalish, 1946, 1947; Blodgett & McCutchan, 1947, 1948; Blodgett, McCutchan, & Matthews, 1949; Thompson & Thompson, 1949; Hill & Thune, 1952; Scharlock, 1955). For example, after animals were trained to enter one arm of a T-maze where they were rewarded with food in a goal box, had they learned a turning response or, alternatively, had they learned where food was located? In order to examine this question, Tolman and colleagues introduced the cross-maze paradigm (Tolman et al., 1946, 1947). The cross-maze is essentially a T-maze built such...
that the choice point connecting the two goal boxes (e.g., east–west), can be approached from start boxes located on either side of the maze (e.g., north–south). During an initial training period, animals are placed in the same start box and trained on several trials to obtain a food pellet from the same goal box. Following this training period, a critical probe trial is given in which animals are placed in the start box opposite the one used during training and allowed to approach either goal box. According to cognitive theory, animals should approach the goal box which was baited during training, since they acquired information concerning the spatial location of the food reward. Animals displaying this behavior on the probe trial are designated “place learners.” In contrast, S-R theory predicts that animals should approach the goal box which was unbaited during training, since they have learned a response tendency (i.e., a specific body turn at the choice point). Animals displaying this behavior are designated “response learners.” Although the cross-maze paradigm provides a procedure to contrast cognitive and S-R learning theories, the findings of many experiments using this task were inconclusive. Under some conditions animals indicated knowledge of the location of rewards (i.e., place learning), and under other conditions they made specific body turn responses on the probe trial (for review see Restle, 1957).

Findings indicating that both place and response learning occurred raises the possibility that these two forms of learning might be mediated by distinct neural mechanisms. This hypothesis is consistent with extensive evidence suggesting that different forms of learning and memory are mediated by different neural systems in humans (e.g., Milner, 1962; Corkin, 1965; Weiskrantz & Warrington, 1979; Cohen & Squire, 1980; Schacter, 1992), monkeys (e.g., Gaffan, 1974; Zola-Morgan, Squire, & Mishkin, 1982; Mahut & Moss, 1984), and rats (e.g., Hirsh, 1974; O'Keefe & Nadel, 1978; Olton, Becker, & Handelmann, 1979; Sutherland & Rudy, 1989). Within the context of the debate between cognitive and S-R learning theorists, it has been suggested that the hippocampal system may selectively mediate “cognitive” memory (Hirsh, 1974; Mishkin & Petri, 1984), and that the caudate nucleus may selectively mediate “S-R habit” formation (Mishkin & Petri, 1984; Packard and White, 1987; Packard, Hirsh, & White, 1989). Similarly, Kesner and colleagues hypothesized that the hippocampus selectively mediates allocentric spatial behavior within a “data-based” memory system, while the caudate nucleus selectively mediates egocentric learning within an “expectancy-based” memory system (Kesner & DiMattia, 1987).

Findings of double dissociations of the effects of brain lesions and intracerebral drug treatments on memory strongly support the hypothesis that the hippocampal system and caudate nucleus mediate different forms of memory. Lesions of the hippocampal system (Packard, Hirsh, & White, 1989; Packard & McGaugh, 1992; McDonald & White, 1993; Kesner, Bolland, & Dakis, 1993), and postraining injections of drugs into the hippocampus (Packard & White, 1991; Packard, Cahill, & McGaugh, 1994), alter cognitive learning but do not affect response learning. Conversely, lesions of the caudate nucleus (Packard et al., 1989; Packard & McGaugh, 1992; McDonald & White, 1993; Kesner et al., 1993), and postraining injections of drugs into the caudate (Packard & White, 1991; Packard et al., 1994), alter response learning but do not affect cognitive learning.

The present study was designed to determine whether the evidence suggesting differential roles of the hippocampus and caudate nucleus in memory might provide a resolution of the place versus response learning question. Rats implanted bilaterally with cannulae in either the hippocampus or caudate nucleus were first trained (four trials per day) using one starting alley of a cross-maze (e.g., south) and consistently rewarded in the goal box of one alley (e.g., west). On Days 8 and 16 the rats were given a single test trial using the other starting alley (e.g., north) to determine whether they made the same turning response made in training or made a different turning response and went to the place where food was located during the training. Prior to the test trials lidocaine or saline was infused bilaterally into either the caudate nucleus or hippocampus. Lidocaine produces a temporary functional blockade of neural activity following local administration in the brain and has been used in studies examining brain function and memory (e.g., Perez-Ruiz & Prado-Alcala, 1989; Salinas, Packard, & McGaugh, 1993). If cognitive and response learning occur in parallel and are mediated by different neural systems, selective temporary inactivation of one of these neural systems prior to testing should influence the type of learning, i.e., place or response learning expressed by the animal on the test trials.

METHODS

Subjects

The subjects were 50 male Sprague–Dawley rats (275–300 g). Animals were individually housed in a temperature-controlled environment on a 12-h light/
dark cycle with the lights on from 7 AM to 7 PM. All animals were given ad lib. access to water.

Apparatus

The apparatus was a wooden cross maze painted flat gray. The maze consisted of four arms (north, south, east, and west) of an eight-arm radial maze (other maze arms were removed). The arms of the cross maze measured 60 x 9 cm. The center platform of the maze connecting the four arms measured 40 cm in diameter. A clear Plexiglas cross-shaped alleyway structure placed on the center platform of the modified radial maze connected the four arms of the cross-maze. The alleyways measured 20 x 9 x 15 cm. A recessed food well was present at the end of the west arm of the maze. The maze was located in a testing room that contained many extramaze cues including wall posters, a lamp, table, animal cage rack, and the seated experimenter.

Surgery

Animals were anesthetized with sodium pentobarbital (50 mg/kg) and implanted with bilateral guide cannulae in the dorsal hippocampus (10 mm length) or dorsolateral caudate nucleus (15 mm length) using standard stereotaxic techniques. The cannulae (23 gauge) were anchored to the skull with jewelers screws and dental acrylic. Coordinates for the dorsal hippocampal placements were AP = -3.1 mm, ML = ± 2.5 mm, and DV = -2.0 mm from bregma. Coordinates for the dorsolateral caudate nucleus placements were AP = -.26 mm, ML = ±4.2 mm, DV = -4.0 mm. After surgery, stylets (30 gauge) were inserted and left in place to ensure cannulae patency until injections were made. Behavioral testing began 1 week after surgery.

Injection Procedures

A 2% lidocaine hydrochloride solution (Western Medical Supply, Inc.) was used to produce reversible inactivation of brain sites. Injections (0.5 µl) were administered intracerebrally using 30-gauge injection needles inserted into the guide cannulae. The needles were connected by polyethylene tubing to 10-µl Hamilton microsyringes (Hamilton Co., Reno, NV). The volume of 2% lidocaine solution used was chosen on the basis of previous evidence indicating that this volume produces functional inactivation of the caudate nucleus (Perez-Ruiz & Prado-Alcala, 1989) and amygdala (Salinas et al., 1993) sufficient to cause memory impairment. Other findings indicate that volumes of 2% lidocaine solution as low as 0.25 µl can produce memory impairment following intracerebral administration (Parent & McGaugh, 1993). The injections were delivered over a period of 37 s using a syringe pump (Sage Instruments), and the injection needles (extending 1 mm from the end of the guide cannulae) were left in place an additional 60 s to allow for diffusion of the solution away from the needle tip. Lidocaine injections were administered approximately 2–3 min prior to the probe trial tests on Days 8 and 16 of training. Saline injections were administered using procedures identical to those used for lidocaine injections.

Histology

At the completion of behavioral training, animals were deeply anesthetized with a 1.0-ml injection of sodium pentobarbital and perfused with saline followed by 10% formal-saline. The brains were removed and subsequently sectioned at 20-µm sections through the cannula tract region and stained with Cresyl violet. Cannula placements were examined for verification of needle tip location using the atlas of Paxinos and Watson (1986).

Cannulae placements for both dorsolateral caudate nucleus and dorsal hippocampus are shown in Fig. 1 (left, right, respectively). Caudate nucleus placements were located in the dorsolateral caudate, ranging from 0.20 mm to -0.30 mm from bregma (Fig. 1, left). Hippocampal placements were located in the dorsal hippocampus, ranging from -2.8 mm to -3.3 mm from bregma (Fig. 1, right).

Behavioral Procedures

Prior to training, all rats were reduced to 85% of ad lib. body weights over 7 days and maintained at this weight throughout the experiment. On 2 consecutive days, rats were placed into the cross-maze in the start box (south arm) and allowed to explore the maze for 5 min. No food was present in the maze on either of these 2 habituation days. Access to the north arm of the cross-maze was blocked during habituation sessions and the subsequent food rewarded training trials with a clear Plexiglas shield. Following habituation on both days, the animals were allowed to consume ten 45-mg Noyes food pellets in their home cage. Food trials began on Day 3. On each food trial rats were placed into the start box and allowed to traverse the maze and consume a single Noyes food pellet located in the food cup at the end of the goal arm of the cross maze (west arm). On the initial food trial only, a trail of four pellets leading to the food cup was placed along the length of the goal arm. Each rat received four food rewarded trials per day. Entries into the unbaited arm of the
FIG. 1. Dorsolateral caudate nucleus (left) and dorsal hippocampus (right) cannulae placements showing the anterior/posterior extent of needle tip locations at 0.5-mm sections. Caudate nucleus placements ranged from 0.20 to 0.30 mm from bregma. Hippocampal placements ranged from −2.8 to −3.0 mm from bregma. (Plates adapted from atlas of Paxinos and Watson, 1986).

Cross-maze (east) were scored as incorrect responses during the training trials, and entries into the baited arm of the cross-maze (west) were scored as correct responses. A correction procedure was used such that rats making an incorrect response were allowed to trace back to the baited maze arm and consume the food pellet. If a rat failed to consume the food pellet within 2 min, the trial was terminated and the rat was manually placed in the goal box and allowed to consume the pellet. After consuming the pellet on a given trial, the rat was placed in a holding cage located directly behind the start arm for a 30-s intertrial interval.

On Day 8 of the food-rewarded trials, rats were assigned to experimental groups (n = 12–14 per group) in a rank-order method to assure that levels of learned performance (i.e., number of correct responses over the first 7 days of training) of the groups were comparable prior to treatment. On Day 8 a single probe trial was given. Three minutes prior to the probe trial, half of the animals with caudate nucleus implants received a saline injection and the other half received a lidocaine injection. Similarly, half of the animals with hippocampal implants received a saline injection prior to the probe trial, and half received an injection of lidocaine. On the probe trial, animals...
were placed into the start box opposite that used during training (i.e., north arm) and were allowed to make a single entry into either the baited or the unbaited maze arm. The entrance to the south maze arm (i.e., the arm containing the start box used during training) was blocked by a clear Plexiglas shield on the probe trials. Animals entering the baited arm on the probe trial were designated "place" learners (i.e., animals going to the place where food was located during training), and animals entering the unbaited arm on the probe trial were designated "response" learners (i.e., animals making the same turning response as during training).

On Day 9 of training, food-rewarded training (four trials per day) was reinstated using procedures identical to those of Training Days 1–7. On Day 16, a second probe trial was given using procedures identical to the probe trial given on Day 8. Animals received the same intracerebral saline or lidocaine treatments given on the Day 8 probe trial and were again allowed to make a single entry into either the baited or unbaited maze arm.

RESULTS

Figure 2 shows the results of the test trials on Days 8 and 16. \( \chi^2 \) analyses (\( p < .05 \) for all comparisons) were computed in order to determine whether groups showed a significant tendency to display place or response learning on the probe trials. On the Day 8 probe trial, animals given saline injections into either the hippocampus or caudate nucleus were predominantly place learners (hippocampus–saline \( \chi^2 = 7.14, p < .05; \) caudate nucleus–saline \( \chi^2 = 5.34, p < .05 \)). Rats given intracaudate injections of lidocaine were also predominantly place learners (\( \chi^2 = 5.34, p < .05 \)), while those receiving intrahippocampal injections of lidocaine did not show a significant trend toward either place or response learning (\( \chi^2 = 0, \text{n.s.} \)). These findings indicate that functional inactivation of the hippocampus, but not caudate nucleus, prevented the expression of place learning.

On the Day-16 probe trial, animals given saline injections into either the hippocampus or caudate nucleus were predominantly response learners (hippocampus–saline \( \chi^2 = 4.58, p < .05; \) caudate nucleus–saline \( \chi^2 = 5.34, p < .05 \)). Rats receiving intrahippocampal injections of lidocaine were also predominantly response learners (\( \chi^2 = 5.34, p < .05 \)), while those receiving intracaudate injections of lidocaine were predominantly place learners (\( \chi^2 = 8.32, p < .05 \)). These findings indicate that with extended training, saline-treated rats switched from displaying place learning to response learning. Functional inactivation of the caudate nucleus, but not hippocampus, prevented the expression of response learning and, in fact, preserved place learning.

DISCUSSION

The results indicate that place and response learning occur concurrently and are mediated by different neural systems involving the hippocampus and caudate nucleus, respectively. The findings are consistent with previous studies using pretraining irreversible lesions of the caudate nucleus (Thompson, Guilford, & Hicks, 1980), and fimbria–fornix (Decastro, 1974), which reported that such lesions result in a predominant tendency toward place and response learning, respectively. Our findings indicate that in addition to acquisition, the functional integrity of the hippocampus and caudate nucleus are necessary for the expression of these two forms of learned behavior.

The finding that rats initially acquire place information and that the expression of such learning is blocked by inactivation of the hippocampus is consistent with extensive evidence implicating the hippocampus in spatial learning (e.g., O’Keefe & Nadel, 1978).

The hippocampal injection sites in the present study were located along the dorsal edge of the hippocampus, and areas of parietal cortex located dorsolateral to the lidocaine injection sites may also be
involved in acquisition of spatial information. For example, large lesions of parietal cortex selectively impair acquisition of a spatial cheese-board task (Kesner, Farnsworth, & DiMattia, 1989) and produce deficits in acquisition and retention of spatial behavior in the Morris water maze (DiMattia & Kesner, 1988). However, the posterior extent of the large parietal cortex lesions reported to impair spatial behavior (Kesner, Farnsworth, & DiMattia, 1989) is approximately 0.5–0.8 mm anterior and 1.0–1.2 mm lateral to our effective injection sites in dorsal hippocampus. Furthermore, small lesions of parietal cortex which may more closely mimic the behavioral effects of any limited spread of lidocaine from hippocampus in the present study do not impair acquisition of spatial behavior in the Morris water maze or the radial maze (Kolb, Sutherland, & Whishaw, 1983). Thus, although the possibility that the spread of lidocaine to adjacent parietal cortex influenced the expression of place learning cannot be completely ruled out, the effect of lidocaine injections on place learning observed in the present study was likely due to neural inactivation of the hippocampus.

The finding that the expression of response learning is blocked by functional inactivation of the caudate nucleus is consistent with the view that the caudate nucleus selectively mediates learning involving the use of “egocentric” cues to guide navigation (Potegal, 1972; Kesner & DiMattia, 1987). For example, lesions of the caudate nucleus impair acquisition of left–right maze discrimination tasks (Cook and Kesner, 1988; Kesner et al., 1993). As the region of the caudate targeted by the lidocaine injections (dorsolateral) receives cortical input from the somatosensory cortex (Heimer, Alheid, & Zarbucky, 1985) such input may be critical for establishing an association between the maze cues and the egocentric cues mediating the specific body turn required for response learning. However, it is important to note that egocentric learning may be but one example of a class of stimulus-response learning functions mediated by the caudate (Packard et al., 1989; Packard and McGaugh, 1992; Viaud & White, 1989), each of which is hypothesized (White, 1989) to be organized on the basis of the sensory cortical input the caudate receives (Heimer et al., 1985).

Rats given saline injections into the hippocampus or caudate nucleus displayed a strong place learning tendency on the Day 8 probe trial. However, animals with the hippocampus inactivated with lidocaine prior to the Day 8 probe trial did not display either place or response learning tendencies. Although the caudate nucleus was presumably functional in these rats, a response learning tendency had apparently not been acquired by this system prior to the eighth day of training. Thus, one difference between the operating characteristics of the hippocampal-based and caudate-based memory systems is that the former system appears to be involved in the rapid acquisition of new information, while the latter system acquires information in a slower, incremental fashion.

With extended training in the cross-maze, animals acquired a response learning tendency (i.e., on the Day 16 probe trial control rats made the same turning response as during training). The finding that the animals shifted from place learning to response learning with increased training is consistent with that of previous research (e.g., Ritchie, Aeschliman, & Pierce, 1950; Hicks, 1964). Importantly, selective functional inactivation of the caudate nucleus prevented the expression of the acquired response and revealed preserved place learning. Thus, the predominance of response learning expressed after extensive training is not due to elimination of the place representation. These findings provide strong evidence that the two memory systems are functioning independently.

In 1957, Restle proposed a resolution of the place versus response learning debate based on findings suggesting that either type of learning could be predicted based on the availability of various extramaze/intramaze cues present (Restle, 1957). Thus, in open mazes located in visually heterogeneous environments place learning is dominant (Blodgett & McCutchan, 1947; Blodgett, McCutchan, & Matthews, 1949; Tolman et al., 1946, 1947), while in closed mazes or visually homogeneous environments response learning is dominant (Blodgett & McCutchan, 1948; Thompson & Tompson, 1949; Hill & Thune, 1952; Scharlock, 1955). According to Restle’s multiple-cue theory, a single learning mechanism was responsible for both place and response learning, and this mechanism was “tuned” to produce either type of learning by the nature of the extramaze/intramaze environment. However, although evidence indicates that the nature of the testing environment contributes to the relative expression of place and response learning, Restle’s resolution of the debate is, at least, incomplete. The nature of the environment appears to interact with separate learning systems in determining the expression of place or response learning. Consistent with this suggestion, acquisition of a caudate nucleus-mediated win–stay radial maze task by intact rats is facilitated when extramaze cues are reduced by surrounding the maze with curtains (Packard & White,
REFERENCES


