Differential effects of immediate posttraining sulpiride microinfusions into the nucleus accumbens shell and core on Morris water maze retention

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Extensive evidence indicates that the nucleus accumbens is involved in spatial learning and memory tasks. There has been relatively little inquiry, however, into which of the two anatomically and functionally distinct subregions of the nucleus accumbens (the shell and the core) mediate this involvement. To investigate this issue, male Sprague–Dawley rats implanted with bilateral intracerebral guide cannulae aimed at the medial shell or core were given eight training trials in the standard hidden platform version of the Morris water maze, immediately followed by intracerebral microinfusions of the D2 dopamine antagonist sulpiride or saline vehicle. A probe trial retention test 2 days later revealed that sulpiride microinfusions into the shell significantly increased latency to reach the platform location, whereas sulpiride microinfusions into the core significantly decreased the time spent swimming near the platform location and significantly increased the time spent swimming in the maze periphery. The results suggest that the nucleus accumbens shell and core may be involved in the consolidation of memory for different aspects of water maze task performance.

As the publication of this issue of Psychobiology demonstrates, there exists a growing appreciation of the role of the nucleus accumbens (NA) in numerous cognitive processes, including learning and memory. Investigation of the mnemonic role of the NA was begun (to our knowledge) by Lorens, Sorenson, and Harvey (1970) and has expanded rapidly in the past several years. The more recent work consists largely of findings that, in both rodents and primates, lesions and drug microinfusions in the NA affect performance in a variety of learning and memory tasks, including the spatial version of the Morris water maze, radial arm maze, spatial discrimination, and avoidance tasks, and several appetitive and aversive classical conditioning tasks (Everitt, Morris, O'Brien, & Robbins, 1991; Gal, Joel, Gusak, Feldon, & Weiner, 1997; Lorenzini, Baldi, Bucharelli, & Tassoni, 1995; McCullough, Sokolowski, & Salamone, 1993; Parkinson, Willoughby, Robbins, & Everitt, 1997; Ploeger, Spruijt, & Cools, 1994; Seams & Phillips, 1994; Stern & Passingham, 1995; Sutherland & Rodriguez, 1989; Westbrook, Good, & Kiernan, 1997; for a partial review, see Setlow, 1997). The effects of NA manipulations cannot easily be attributed to perceptual, motor, or motivational changes, because it has been demonstrated in several studies that the same NA manipulations that affect performance in the tasks listed above have no effects in other, related tasks with similar performance demands (e.g., the cued version of the Morris water maze or a visual discrimination task; Seams & Phillips, 1994; Stern & Passingham, 1995; Sutherland & Rodriguez, 1989; Westbrook et al., 1997).

In addition to controlling for the effects of NA manipulations on nonmnemonic components of task performance, these dissociations suggest that the NA is involved only in specific forms of learning and memory and not in others, as has been demonstrated for other brain regions, such as the hippocampal formation (Packard, Cahill, & McGaugh, 1994; Squire & Knowlton, 1994). This suggestion is consistent with evidence concerning the sources of cortical inputs to the NA (such as the hippocampal formation, the basolateral complex of the amygdala, and the cingulate cortex), which mediate learning and memory in the tasks listed above and in which manipulations produce many of the same effects that are found with NA manipulations (Everitt et al., 1991; McGeorge & Faull, 1989; Packard & White, 1991; Parkinson et al., 1997; Seams & Phillips, 1994; Sutherland & Rodriguez, 1989). This relationship has been made explicit in several studies reporting that asymmetric contralateral lesions of the NA and one of its cortical afferents produce the same pattern of effects on learning and memory as do bilateral NA or cortical afferent lesions (Everitt et al., 1991; Floresco, Seams, & Phillips, 1997; Parkinson et al., 1997).

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Recent work from our laboratory provides additional evidence for a mnemonic role of the NA. Microinfusions of the D2 dopamine receptor antagonist sulpiride into the NA immediately following training impaired retention 2 days later (as assessed by latency to reach the platform location) in the spatial but not in the cued version of the Morris water maze (Setlow & McGaugh, 1998). These results not only reinforce the idea that the NA is involved in forms of learning and memory related to those associated with its cortical afferents (in this case, presumably the hippocampal formation), but also, through the use of a posttraining, temporary manipulation, provide evidence that the NA is involved in consolidation of this form of memory.

In the majority of the experiments described above, the lesions or drug microinfusions in the NA affected the entire structure. The NA consists of two distinct subregions, however, termed the core and shell, which differ in their neurochemistry and patterns of connections with other brain regions (Heimer, Zahm, & Alheid, 1995). These two subregions also differ in their involvement in several aspects of behavior, including performance in learning and memory tasks (Carlezon & Wise, 1996; Maldonado-Irizarry & Kelley, 1995b; Sokolowski & Salamone, 1998; Weiner, Gal, Rawlins, & Feldon, 1996). For example, in rats, intracore microinfusions of glutamate receptor antagonists were more disruptive to performance in a spatial food-search task than were intrashell microinfusions (Maldonado-Irizarry & Kelley, 1995a).

In our previous paper (Setlow & McGaugh, 1998), we suggested that the effects of sulpiride on water maze retention might be due primarily to disruption of memory consolidation processes in the core. This speculation was based on the work of Maldonado-Irizarry and Kelley (1995a), described above, as well as on the fact that our microinfusions were centered within this subregion. The present experiment sought to address this issue explicitly, through the use of sulpiride microinfusions administered into the core or shell immediately after training in the spatial version of the Morris water maze. An additional goal of these experiments was to explore the involvement of the shell and core in memory for different aspects of the water maze task. Successful water maze performance requires memory not only for the spatial location of the hidden platform, but also for nonspatial, or "procedural", components of the task, such as swimming away from the walls of the maze (Devan, Goad, & Petri, 1996). These components, of which there are probably several, seem to be anatomically and pharmacologically dissociable from memory for the platform location (Bannerman, Good, Butcher, Ramsay, & Morris, 1995; Devan et al., 1996). Accordingly, several measures of retention were used, in an attempt to assess the involvement of the shell and core in consolidation of memory for different task components.

**METHOD**

The methods have been described previously (Setlow & McGaugh, 1998).

**Animals**

The subjects were 93 male Sprague–Dawley rats (Charles River, San Diego) weighing 225–250 g upon arrival. They were individually housed in a temperature-controlled colony room (22°C) and maintained on a 12:12-h light:dark cycle (6 a.m.–6 p.m., lights on) with ad-lib access to food and water.

**Surgery**

Approximately 1 week after their arrival, the rats were anesthetized with sodium pentobarbital (65 mg/kg i.p. Nembutal, Abbott Laboratories, Chicago), which was supplemented with methoxyflurane (Mefo) as needed, and were given atropine sulfate (0.05 mg, i.p.) to maintain respiration. Their skulls were fixed to a stereotaxic frame (Kopf Instruments, Tujunga, CA), a midline incision was made, and holes were drilled in the skull for cannulae and three anchoring screws. Guide cannulae (23 ga., 15 mm) were implanted bilaterally above the NA shell or core (flat skull coordinates from bregma—shell: AP, +1.7 mm; ML, ±0.9 mm; DV, −5.2 mm from skull; core: AP, +1.7 mm; ML, ±1.9 mm; DV, −5.2 mm from skull). The guide cannulae were affixed to the skull and the anchoring screws with dental cement, and the incision was closed with wound clips. Immediately after surgery, the rats received injections of penicillin (0.05 ml, i.m.) and physiological saline (3 ml, s.c.) and were placed in a temperature-controlled incubator until they recovered from anesthesia. Stylets (15 mm, 00 insect pins) were inserted into the guide cannulae to maintain patency.

**Apparatus**

The water maze was a circular black-painted metal tank (1.83 m in diameter, 0.58 m in height), the floor of which was raised 60 cm above the room floor. It was located in a room (3 X 3.6 m) containing several extra-maze cues (including the door, cabinets, and several posters on the walls) and was filled with water (25°C ± 1°C) to a depth of 22 cm. Four start positions (labeled N, S, E, and W) were used. Each start position was used twice. On each training trial, the rats were placed into the water, facing the wall of the maze at one of the start positions in a pseudorandom order so that each of the four start positions was used twice. Each rat was allowed to search for the platform for 60 sec, after which it was gently guided to the platform. Behavioral data were recorded via an OMRON electronic stop watch.

**Drug Microinfusions**

(--)-Sulpiride (Sigma, St. Louis, MO) was dissolved in 0.9% saline. Although sulpiride is usually dissolved in slightly acidic solutions, we found that, at the low concentrations used here, it went into solution with extensive stirring. Saline alone was used for control microinfusions. All microinfusions were administered in a volume of 0.3 µl/side through bilateral needles (30 ga., 17 mm) placed in the guide cannulae. The needles were attached by lengths of plastic tubing (PE 20) to 10-µl syringes (Hamilton, Reno, NV), which were mounted on a timer-controlled infusion pump (Sage Instruments, Boston). Microinfusions took place over 35 sec, after which the needles were left in place for 60 sec to allow for diffusion.

**Behavioral Procedures**

The rats were allowed to recover for at least 1 week following surgery, during which they were handled three times for 1 min each. All the procedures were carried out between 10 a.m. and 3 p.m. Training consisted of a single session of eight trials, with the start positions in a pseudorandom order so that each of the four start positions was used twice. On each training trial, the rats were placed into the water, facing the wall of the maze at one of the start posi-
Figure 1. Microinfusion needle tip locations in the nucleus accumbens. A: locations in shell animals. B: locations in core animals. Plates adapted from The Rat Brain in Stereotaxic Coordinates (Figures 9-14), by G. Paxinos and C. Watson, 1997, San Diego: Academic Press. Copyright 1997 by Academic Press. Adapted with permission.

Histology
After testing, the rats were given an overdose of pentobarbital and perfused intracardially with 0.9% saline followed by 4% formaldehyde, and their brains were removed and stored in 4% formaldehyde. The brains were then sliced on a freezing microtome, and coronal sections (80 μm) were collected through the area of the NA. Sections were mounted on glass slides, stained with thionin, and coverslipped with Permount. Placements of the microinfusion needles were verified under a light microscope by an observer blind to drug treatment condition and were mapped onto plates adapted from the atlas of Paxinos and Watson (1997).

Statistics
Training latencies were analyzed using repeated measures analyses of variance (ANOVAS), with training trial as the within-subjects variable and drug treatment as the between-subjects variable. Retention data were analyzed using one-factor ANOVAs, with drug treatment as the between-subjects variable. Post hoc comparisons between groups were done with Fisher's PLSD. In all cases, p values less than .05 were considered significant. Outliers, defined as scores outside the range of ±2 SD from the group mean, were excluded from each group prior to statistical analysis. The following scores were excluded on these grounds. Platform location latency: shell, one each in the saline and 10-ng sulpiride groups; core, one in each group. Annulus time: shell, one each in the 10- and 100-ng sulpiride groups; core, one in the 10-nm sulpiride group. Periphery time: core, one in the 100-ng sulpiride group. Path length: shell, one each in the saline and 10-ng sulpiride groups; core, one each in the saline and 10-ng sulpiride groups.

RESULTS

Histology
Microinfusion needle placements for the shell and core animals are shown in Figure 1. Eighteen animals (9 shell
Behavior

Acquisition. Repeated measures ANOVAs revealed a significant effect of training trial in both the shell \(F(7,238) = 25.02, p < .0001\) and the core \(F(7,245) = 45.06, p < .0001\) animals. There were no significant between-group differences, however, in either the shell \(F(2,34) = 0.51, p > .05\) or the core \(F(2,35) = 0.63, p > .05\) animals prior to drug treatment (Figure 2).

Retention. One-factor ANOVAs (with drug treatment as the between-subjects variable) revealed a significant drug effect on the platform location latency measure in the shell \(F(2,32) = 4.02, p < .05\) but not in the core \(F(2,32) = 0.36, p > .05\) animals (Figure 3A). Post hoc tests showed that, in the shell animals, the 100-ng/side sulpiride group had significantly longer latencies than the saline group \((p < .01)\). On the annulus time measure, one-factor ANOVAs revealed a significant drug effect in the core \(F(2,34) = 3.65, p < .05\) but not in the shell \(F(2,34) = 1.58, p > .05\) animals (Figure 3B). Post hoc tests showed that, in the core animals, the 10-ng/side sulpiride group spent significantly more time in the maze periphery than did the saline group \((p < .05)\). Finally, on the path length to the platform location measure, one-factor ANOVAs revealed a significant effect of sulpiride in the shell \(F(2,32) = 4.74, p < .01\) but not in the core \(F(2,33) = 0.08, p > .05\) animals (Table 1). Post hoc tests showed that, in the shell animals, the 100-ng/side group had significantly longer path lengths to reach the platform location than did the saline group \((p < .01)\).

Discussion

The results showed that immediate posttraining microinfusions of sulpiride into the NA shell or core impaired different measures of retention in the spatial version of the Morris water maze. Specifically, sulpiride microinfusions into the shell impaired retention only on the platform location latency measure (as well as on the related path length measure), whereas microinfusions into the core impaired retention only on the annulus time and periphery time measures. These findings suggest that both the shell and the core are involved in consolidation of memory for the Morris water maze, but for different aspects of the task.

The performance of shell and core cannulated animals was largely similar during both acquisition and retention following saline microinfusions. There was, however, a significant difference between the platform location latencies in the saline control groups in shell and core animals (see Figure 3A). The cause of this difference is unclear, although it is likely that it is due to differences in the effects of cannula implantation in the shell and core. It should be noted that these differences are probably not attributable to general motor or cognitive impairments in the core animals, however, since there were no significant differences between shell and core saline groups, either in their acquisition latencies or in their annulus or periphery times (and, in fact, the core-saline group performed better than the shell-saline group on the annulus time measure). Regardless of the cause of this difference, it raises the possibility that the high platform location latencies of the saline control group in the core animals may have obscured an impairing effect of sulpiride microinfusions into the core on this measure. However, we believe that this explanation is inadequate for two rea-
sons. First, in our previous study employing whole NA microinfusions (Setlow & McGaugh, 1998), the mean platform location latency of the rats given the most effective dose of sulpiride was 40 sec, suggesting that a ceiling effect did not obscure an impairing effect of sulpiride in the core animals in the present study. Second, we have found that, in animals given spatial pretraining in a different water maze prior to training and testing in the water maze used here (and in which the platform location latencies of the saline groups were equivalent in shell and core animals), sulpiride was also only effective in shell animals (Setlow & McGaugh, unpublished data).

The dissociation suggested here between mnemonic functions of the shell and those of the core is consistent with evidence showing that the two subregions are differentially involved in several behaviors (Maldonado-
Despite the unexpected absence of an effect of core sulpiride microinfusions on the platform location latency measure, it is interesting to note that the pattern of impairments found in the core animals on the three retention measures (impairment on the annulus and periphery time measures, but not on platform location latency) is identical to that produced by sulpiride microinfusions into the posteroverventral caudate-putamen (Setlow & McGaugh, 1999). We previously proposed that this pattern of results represents impaired memory for procedural aspects of water maze performance. For example, an impairment in memory for the strategy “persist in searching away from the wall if you don’t find the platform immediately” would produce the pattern of impairments observed in core animals (Setlow & McGaugh, 1999). It should be pointed out that annulus time (and similar proximity measures, such as quadrant time) is usually thought to measure the same aspect of behavior (memory for the platform location) as does the latency measure, and in many cases (e.g., Markowska, Long, Johnson, & Olton, 1993), this is probably true. Given that performance on the two measures seems to be dissociable, however, in a manner inconsistent with floor or ceiling effects on either measure (Setlow & McGaugh, 1999; present study), it seems that the most parsimonious interpretation of these results is that, under the training conditions used here, the annulus and latency measures assess memory for different aspects of task performance.

The finding that the core and caudate-putamen are similarly involved in Morris water maze retention is not surprising in light of the anatomical similarity between these two areas of the striatum (Heimer et al., 1995). Further support for this similarity is found in a recent study in which core microinfusions of an NMDA-receptor antagonist in rats impaired acquisition of an operant barpress task that is also affected by manipulations of the caudate-putamen (Kelley, Smith-Roe, & Holahan, 1997; Prado-Alcalá, Kaufman, & Moscona, 1980). Interestingly, the dissociation seen in the present study between the shell and core is similar to that which has been observed between the hippocampus and the caudate-putamen (Packard & Teather, 1997; Setlow & McGaugh, 1999).

The proposed differences between the mnemonic functions of the shell and those of the core raise the question of which inputs to these parts of the striatum might mediate these functions. It has been known for some time that different regions of the striatum are often involved in cognitive functions (including learning and memory) in a manner similar to the involvement in these same functions of their cortical afferents (Levy, Friedman, Davachi, & Goldman-Rakic, 1997; Rolls, 1994; Rosvold, 1972). Application of this principle to the NA suggests that the different mnemonic functions of the shell and core proposed here may be mediated by different sets of cortical afferents. Notably, the involvement in Morris water maze memory of two NA-projecting cortical areas shows some parallels with the involvement of

| Path Length Swum to Platform Location on the Retention Test | Group | M (in cm) | ±1 SEM |
|-------------------------------------------------------------|-------|-----------|--------|
| Core                                                        | salmine | 490.0     | 129.5  |
| 10 ng/side                                                  | 438.0  | 102.1     |
| 100 ng/side                                                 | 507.9  | 128.5     |
| Shell                                                       | salmine | 148.2     | 29.4   |
| 10 ng/side                                                  | 365.8  | 97.2      |
| 100 ng/side                                                 | 652.5* | 166.0     |

*p < .01, as compared with shell-saline group.
the shell and the core in this task. Immediate posttraining microinfusions of AP-5 into the hippocampus impair latency to reach the platform location (Packard & Teather, 1997). In contrast, immediate postraining microinfusions of AP-5 into the insular cortex impair retention on a proximity measure (number of platform crossings) similar to the annulus time measure used here, but not on latency to reach the platform location (Gutiérrez, Hernández, Ramírez-Amaya, & Bermúdez-Rattoni, 1999). It is interesting to speculate that afferents from these two structures may mediate the differential effects of sulpiride in the shell and core, although, clearly, direct comparisons using our measures would be necessary for a more definitive conclusion. Moreover, the potential for emergent mnemonic properties arising from convergence of cortical inputs in the NA must be considered.

The results of this experiment indicate that the NA is involved in consolidation of memory for the water maze. They do not, however, address the question of whether the NA is a site of storage for this memory. NA lesions and intra-NA microinfusions of haloperidol, both of which severely disrupt acquisition in the water maze, have little or no effect on performance in rats that have already acquired the task (Ploeger et al., 1994; Sutherland & Rodriguez, 1989). These findings suggest that the NA is not a permanent site of storage for water maze memory, or at least that alternative, non-NA-dependent storage sites become available following training. Thus, it is possible that the sulpiride microinfusions in the present study affected memory storage through influences elsewhere in the brain—potentially in cortical areas to which the NA projects through pallido-thalamo-cortical connections (Alexander, Crutcher, & DeLong, 1990; Groenewegen, Berendse, Wolters, & Lohman, 1990; Setlow, 1997).

In conclusion, the results of this experiment showed that immediate postraining microinfusions of sulpiride into the shell and the core subregions of the NA differentially affected several measures of retention in the Morris water maze. Shell microinfusions impaired latency to reach the platform location, but not annulus or periphery time, whereas core microinfusions produced the opposite pattern of results. These results provide evidence for functional differences between the NA shell and core and highlight the importance of differentiating between the two subregions in studies of mnemonic functions of the NA.

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