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Photothrombotic Lesions of the Rat Cortex Impair Acquisition of the Water Maze

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ROGERS, D. C. AND A. J. HUNTER. *Photothrombotic lesions of the rat cortex impair acquisition of the water maze.* PHARMACOL BIOCHEM BEHAV **56**(4) 747–754, 1997.—Photochemical induction of a thrombosis produces lesions of the cortex of reproducible area and depth, and it has been suggested that this may provide a relatively noninvasive model of the human condition of stroke. The cognitive effects of photothrombotic lesions centred at two different positions were assessed in rats using the Morris water maze test for spatial learning and memory, and it was demonstrated that profound deficits in acquisition of this task were produced by bilateral lesions of the frontal cortex. These effects were in the absence of overt motor deficits, and there was no significant correlation between lesion volume and functional deficits. Flunarizine (2 mg/kg) did not attenuate this ischaemic damage and had no effect on the functional deficits. This model has distinct advantages over more invasive global models of ischaemia and may also provide greater understanding of the functional role of the mammalian neocortex. © 1997 Elsevier Science Inc.

Photothrombosis Ischaemia Frontal cortex Spatial memory Water maze Rat

STROKE is the third greatest cause of death in the industrialised world. Although changes in risk factor levels and improvements in both diagnosis and medical management have contributed to a marked decline in death rates, the incidence has not declined; each year, for example, 500,000 stroke cases are reported in the United States alone (1). Cerebral ischaemia may be defined as a deficiency of the blood supply to part of the brain, which produces a cerebral infarction; there is a long list of symptoms and signs of stroke that are determined by the size and location of the infarct. These range from neck stiffness, nausea, and headache to blurred vision, vertigo, dizziness, convulsions, and loss of consciousness. There are also a wide range of motor and sensorimotor deficits, including tremor, lack of coordination, and partial paralysis. In addition, higher cortical dysfunction is also manifested as amnesia, dementia, and delirium, as well as language and speech disturbances, and patients surviving a stroke may be severely mentally and physically disabled. Traditionally, the major focus in stroke rehabilitation has been on physical motor function, although cognitive and emotional deficits make a significant contribution to the quality of life of the patient, relatives, and caregivers. The recognition of vascular dementia (15) and its association with the spiralling costs of health care have meant that the cognitive deficits associated with ischaemia are becoming increasingly important: cognitive impairment has been reported in 35% of patients with stroke compared with less than 4% of age-matched controls (30).

There is increasing interest, therefore, in the functional consequences of ischaemic damage in preclinical models, and the effects on learning and memory in global models of ischaemia in the rat have been well documented (23). Although the unilateral nature of a focal middle cerebral artery occlusion (MCAO) has largely restricted such studies to measurement of motor and sensorimotor deficits, there have also been reports of cognitive deficits in these models (2,20,25,28). The development of the rose bengal photochemically induced cerebral thrombosis model first described by Dietrich and colleagues (12) and Watson and colleagues (34), has enabled reproducible thrombotic infarction of the rat cerebral cortex. Systemic administration of the photosensitizing dye, rose bengal, followed by exposure to high-intensity light through the skull, produces photochemically induced endothelial damage followed by marked platelet aggregation that results in cortical microvascular stasis (11,12). This is now well characterised as an alternative focal ischaemia model (3,5,8–10,16,31,32).

Photothrombotic ischaemia has been used previously to demonstrate both sensorimotor (7) and cognitive (6,17,27,29) deficits in the rat. The ability to place the lesion at a given cortical location confers upon the photothrombotic model the ability to assess cognitive deficits following ischaemia and to

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investigate the effects of potential neuroprotective compounds on the functional recovery of specific neuronal systems. We have demonstrated previously that rose bengal lesions of the frontal cortex produce deficits in the delayed nonmatching to position operant task in rats (27), and in the present study we have investigated the effect of photothrombotic lesions of two different cortical regions on the spatial learning ability of rats in the water maze. In addition, we have tested the calcium channel antagonist flunarizine, a potential neuroprotective agent that has been reported previously to attenuate sensorimotor deficits in this lesion model (7). The results demonstrate that lesions of both the frontal and frontal/parietal cortical areas produce marked impairments in acquisition of this task.

METHOD

Induction of Photothrombotic Ischaemia

Bilateral focal photothrombotic ischaemic lesions of the cortex were made by systemic injection of rose bengal dye followed by exposure of the skull to high-intensity light; all procedures were reviewed by a SmithKline Beecham internal ethics committee. Male Lister hooded rats (250–300 g; OLAC, Bicester, UK) were housed in groups of four to six prior to surgery and maintained under a natural 12 L : 12 D cycle with food and water available ad lib. After surgery, the animals were housed in individual cages with paper bedding, and their diet was supplemented with soft mash for the first 48 h.

The rats were anaesthetised with halothane (3–5% in 95% O_2/5% CO_2) and placed in a Kopf stereotaxic frame. Anaesthesia was maintained by a purpose-built mask that fitted over the incisor bars. Body temperature was kept constant by a heated mat controlled by a rectal temperature probe. The scalp was retracted to expose the skull and a cannula inserted into the lateral tail vein. The photosensitive dye, rose bengal (20 mg/ml saline; Aldrich, Gillingham, UK), was slowly infused over the course of 1 min in a dose volume of 1 ml/kg. The skull was illuminated by means of a fibre-optic bundle (3 mm diameter) for 5 min at coordinates 2.2 mm anterior to the bregma and 2.0 mm left and then 2.0 mm right of the midline. A xenon arc lamp (300 W; Oriel, Leatherhead, UK) provided the light source and was focused through a water filter to remove heat. Sham animals received saline and were exposed to the high-intensity light. The rats were removed from the frame, sutured, and allowed to recover under a heat lamp before being returned to their home cages.

In a subsequent study, lesions were induced via a bifurcated fibre-optic light guide. This was positioned above the bregma in a holder designed to locate the heads of the light guide 2.5 mm to the left and right of the midline. All other aspects of the procedure were as detailed above.

Acquisition of the Water Maze

The Morris water maze (21,22) was used to assess the spatial learning and memory capacity of rats following photothrombotic lesions. In this procedure, the animals were required to locate a submerged platform using distal cues surrounding the pool.

The water maze consisted of a white Perspex pool 200 cm in diameter and 50 cm high. It was filled with water to a depth of 40 cm, and the water was made opaque by addition of a latex compound. The pool circumference was arbitrarily marked with start positions—north, south, east, west (N, S, E, W)—and divided into four imaginary quadrants (1–4). A platform was placed in the centre of quadrant 1. The platform (a 10-cm colourless Perspex disk) was anchored 2 cm below the surface and was invisible to the rat swimming in the water. Surrounding the pool were various visual cues, including screens and wall posters. A video camera was positioned directly above the pool and connected to an HVS-image analyser, which transformed the normal video image into a picture of high-contrast edges. This was in turn linked to an IBM-compatible personal computer, which stored measurements of latency, path length, and percent time spent in each quadrant for each trial.

Four days after surgery, the rats began training in the water maze. Over the next 4 days, each animal received 22 training trials randomised across the four different start positions. At the beginning of each trial, the rat was lowered gently feet first into the water, facing the wall at a start position (N, S, E, or W) that had been predetermined randomly. A remote control was used to activate the computer, and the rat was allowed to swim for 100 s to find the platform. If the platform was found during this time, the trial was stopped, the recording was terminated by remote control, and the rat was left on the platform for 10 s. If the platform was not found during this time, the rat was retrieved quickly from the water and placed on the platform for 10 s. After each trial, the rat was dried briefly with a towel. Each rat received four consecutive trials on day 1 of training and six trials on days 2 and 3. On day 4, each rat received six trials followed by a probe trial (transfer test). For the probe trial, the platform was removed from the pool and the rat was allowed to swim for 100 s. The proportion of time spent in the platform quadrant during the probe trial provided an assessment of how well each rat had learned the position of the platform. Acquisition of the platform position by each rat was quantified by analysis of latency to find the platform, path length of each trial during the training procedure, and percent time spent in the platform quadrant during the probe trial. The swim speed (cm/s) of each rat during trial 1 on the first day of training was calculated by dividing the path length by the latency.

This procedure was modified subsequently by reducing the maximum length of any one trial to 60 s. In addition, the original smooth 10-cm platform was replaced by a slightly larger version (15 cm diameter) that had a ribbed surface. All other aspects of the procedure were as detailed above.

Histology

After behavioural assessment, the animals were perfusion fixed intracardially with buffered formalin under terminal barbiturate anaesthesia. The brains were removed and serial coronal sections (60 μm) were stained with haematoxylin and eosin. The lesion area in each section was determined by digital planimetry, using a Quantimet 920 image analysis system (Leica Ltd., Milton Keynes, UK), and the total lesion volumes were calculated by Simpson's rule for numerical quadrature. The extent of the lesions was determined with reference to the Zilles stereotaxic atlas (36).

Statistical Analysis

Measurements of latency and path length were blocked by day, and statistical comparisons between groups were carried out by repeated measures analysis of variance (ANOVA) using SAS-RSA (Research Scientists Application, SAS Software Ltd.). Comparisons between groups for probe trial data were carried out by one-way ANOVA followed, where appropriate, by Tukey's test for pairwise comparison of means.

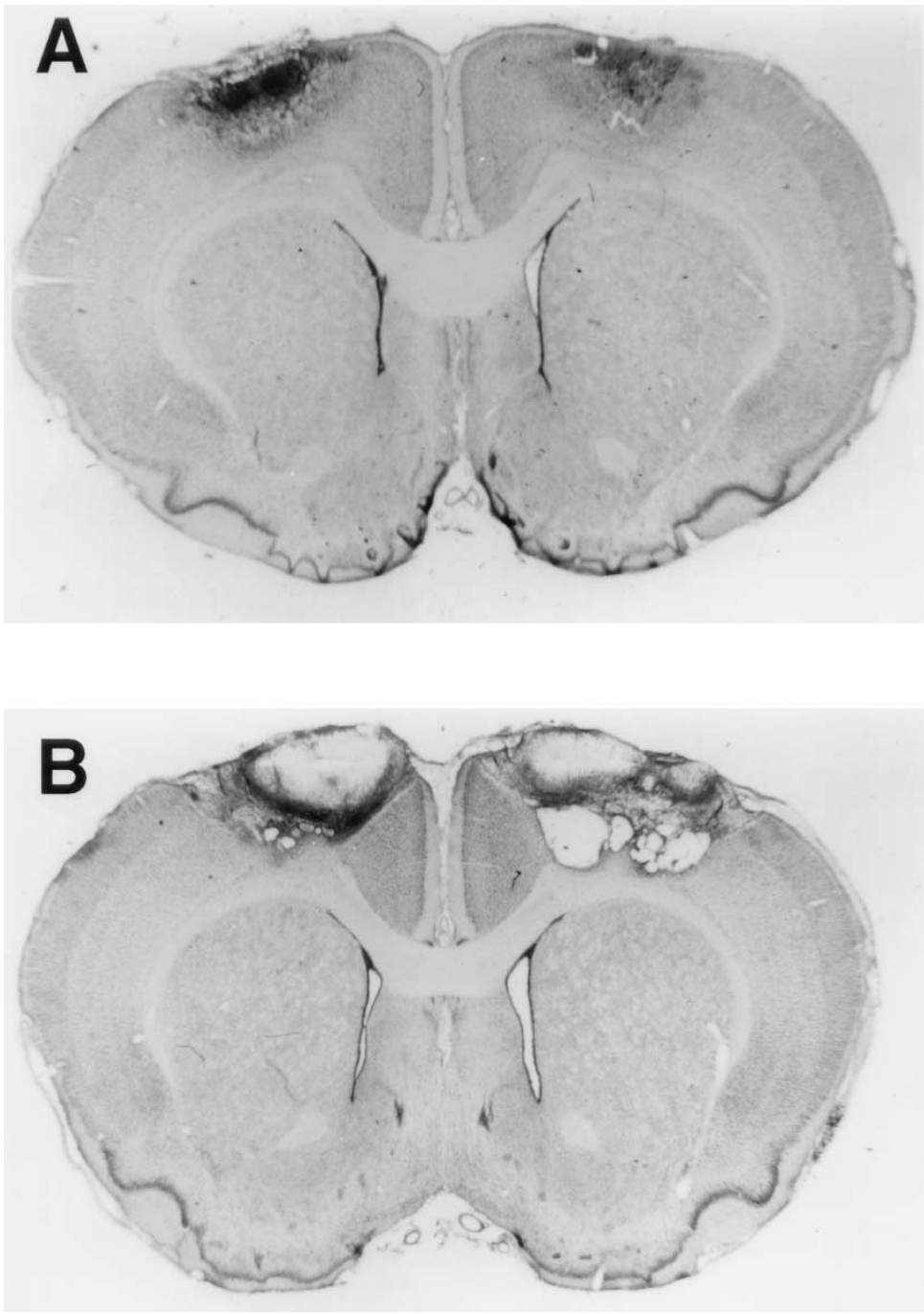

FIG. 1. Photomicrographs representative of the necrotic zone following photothrombotic lesions of the cortex. (A) Frontal cortex lesion at the level of 1.7 mm anterior to the bregma. (B) Bregma-level lesion at the level of 1.0 mm anterior to the bregma. Sections stained with haematoxylin and eosin.

RESULTS

Histology: Frontal Cortex Lesion

In all experiments, the photothrombotic thrombosis produced discrete, hemispherical cortical lesions that were maximal in surface area at the cortical surface, and at the midpoint extended in depth to the corpus callosum. Histopathological assessment of the frontal cortex lesions from the first experiment revealed a mean total lesion volume of 8.3 ± 1.1 mm^3 (range 5.3–12.5 mm^3). No evidence of lesions was found in the brains of animals from the sham lesion group. Lesions in the left hemisphere were larger than in the right and, in general, were also slightly posterior to the centre of the fibre-optic placement. The rostral/caudal limits of the lesions ranged from 4.7 mm anterior to the bregma to 1.3 mm posterior to the bregma. In all cases, the primary motor areas (Fr1 and

Fr3) were the areas most damaged (Fig. 1A). Variable damage was observed in the dorsal anterior cingulate cortex (Cg1) and the supplementary motor cortex (Fr2), and there was occasional damage to the parietal cortex (Par1), with some encroachment into the forelimb (FL) and hindlimb (HL) areas, and occasional glial infiltration of the dorsal striatum. All other cortical areas, including the agranular (RSA) and granular (RSG) retrosplenial cortex and occipital cortex were spared. There was no evidence of damage in any subcortical area such as the hippocampus, fornix, caudate, or anterior thalamic nuclei.

Histological examination of the brains from the flunarizine experiment revealed that there was no significant difference between the lesion volumes of the lesion and flunarizine groups of animals, which had total lesion volumes of 5.5 ± 1.0 mm^3 (range 1.3–6.9 mm^3) and 5.2 ± 0.6 mm^3 (range 3.3–7.0 mm^3), respectively ($t_{13} = 0.28$, $p = 0.79$). No evidence of lesions was found in the brains of animals from the sham lesion group. Lesions in the left hemisphere were larger than in the right and, in general, were also slightly posterior to the centre of the fibre-optic placement. The rostral/caudal limits of the lesions ranged from 3.2 mm anterior to the bregma to 0.8 mm posterior to the bregma. As above, the primary motor areas (Fr1 and Fr3) were the areas most damaged. Variable damage was observed in the dorsal anterior cingulate cortex (Cg1) and the supplementary motor cortex (Fr2), and there was occasional damage to the forelimb (FL) and hindlimb (HL) areas and occasional glial infiltration of the dorsal striatum. All other cortical areas, including the parietal cortex, the agranular and granular retrosplenial cortex, and occipital cortex were spared. There was no evidence of damage in any subcortical area such as the hippocampus, fornix, caudate, or anterior thalamic nuclei.

Histology: Bregma-Level Lesion

Histological examination of animals from the first experiment in which the lesion was centred at bregma, revealed that the lesioned group had a total lesion volume of 13.3 ± 2.9 mm^3 (range 4.8–20.6 mm^3). Histological examination of animals from the experiment with the modified platform revealed that the lesioned group of animals had a total lesion volume of 12.7 ± 2.4 mm^3 (range 4.0–25.4 mm^3). In both cases, no evidence of lesions was observed in the brains of animals from the sham-lesion group. The rostral/caudal limits of the bregma-level lesions ranged from 2.2 mm anterior to the bregma to 3.3 mm posterior to the bregma. In all cases, the forelimb (FL), hindlimb (HL), and primary motor (Fr1 and Fr3) areas were the most damaged (Fig. 1B). Variable damage was observed in the cingulate cortex (Cg1 and Cg2), with some encroachment into the supplementary motor area (Fr2), and occasional damage to the parietal cortex (Par1). As described above, all other cortical areas and all subcortical areas were spared.

Water Maze Acquisition: Effect of Frontal Cortex Lesion

Eighteen rats received sham ($n = 8$) or rose bengal ($n = 10$) lesions of the frontal cortex as described above, and training in the water maze began 4 days after surgery. The rose bengal injection produced necrosis in the tail of two animals, which were excluded from the study. Acquisition of the platform position in the water maze task was significantly impaired in the lesion group (Fig. 2). Analysis of variance revealed a significant treatment effect on the latency to find the platform

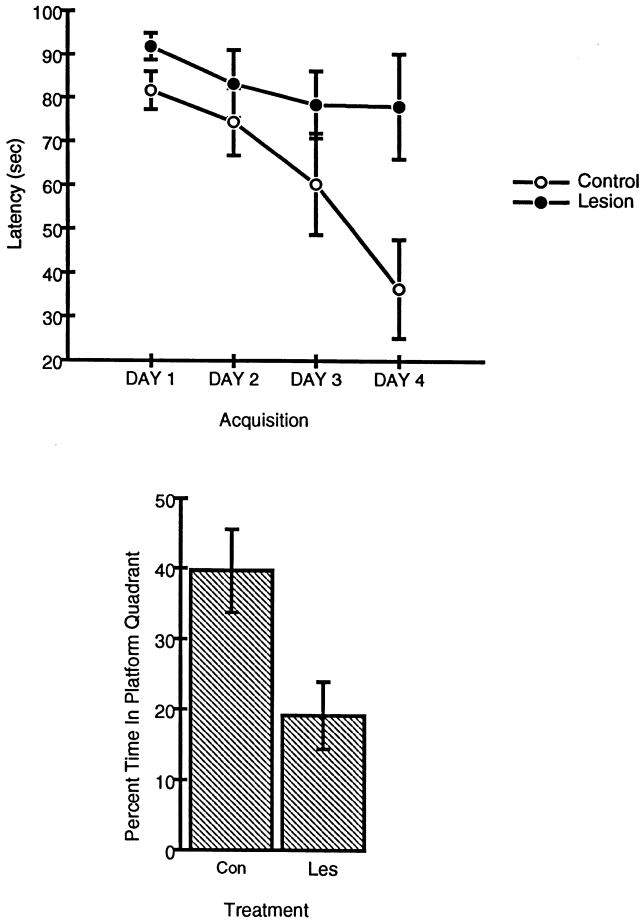

FIG. 2. Effects of photothrombotic lesions of the frontal cortex on acquisition of the water maze ($n = 8$). Top panel: Latency to find platform (mean ± SEM of each rat's trials blocked across day). Bottom panel: Percent time spent in platform quadrant during probe trial (mean ± SEM).

[Groups, $F(1, 13) = 6.04$, $p = 0.029$]. There was also a significant effect of day [Day, $F(3, 39) = 7.85$, $p < 0.001$] and a significant interaction between treatment and day [Groups × Day, $F(3, 39) = 2.89$, $p = 0.048$]. This impairment of learning was further indicated by the percent time spent in the platform quadrant during the probe trial (Fig. 2). There was a significant difference between the control and lesion groups ($t_{15} = 2.36$, $p = 0.033$). During the first training trial, there was no significant difference in the swim speed between the control (22.0 ± 0.9 cm/s) and the lesion (25.2 ± 3.7 cm/s) groups.

Water Maze Acquisition: Effect of Flunarizine on Frontal Cortex Lesion

Twenty-four rats received either sham ($n = 8$) or rose bengal ($n = 16$) lesions as described above. Eight rats that were to receive a lesion were injected with the nonselective calcium channel antagonist flunarizine dihydrochloride (2 mg/kg IP; Sigma) in a dose volume of 2 ml/kg 30 min prior to surgery and 30 min postsurgery. Each rat in the flunarizine group then received a similar injection once per day for 3 days after surgery. One animal from the sham-lesion group developed a scalp infection and was excluded from the study.

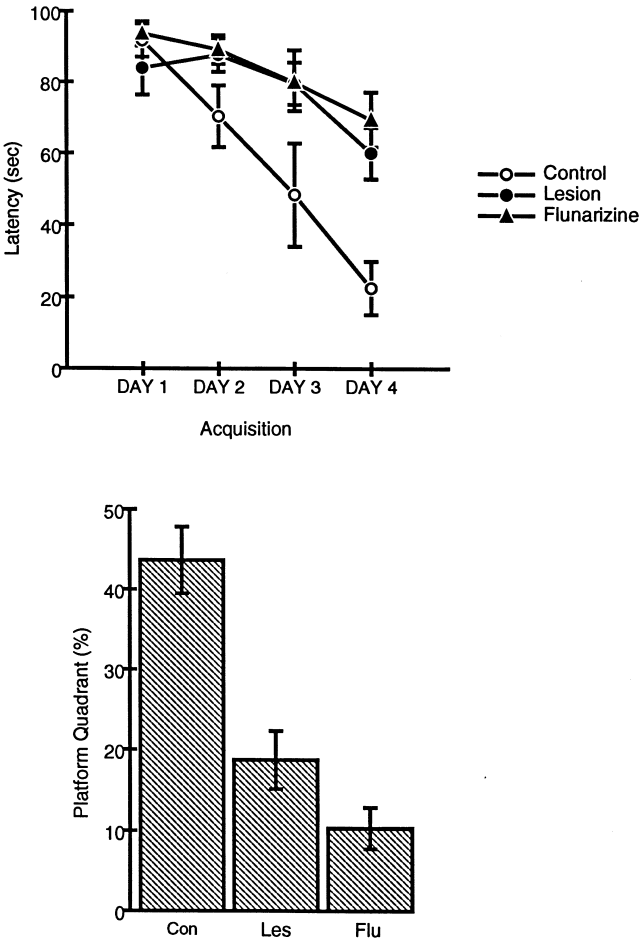

FIG. 3. Effects of flunarizine (2 mg/kg) on photothrombotic lesion-induced deficits in acquisition of the water maze (n = 7 or 8). Top panel: Latency to find platform (mean ± SEM of each rat's trials blocked across day). Bottom panel: Percent time spent in platform quadrant during probe trial (mean ± SEM).

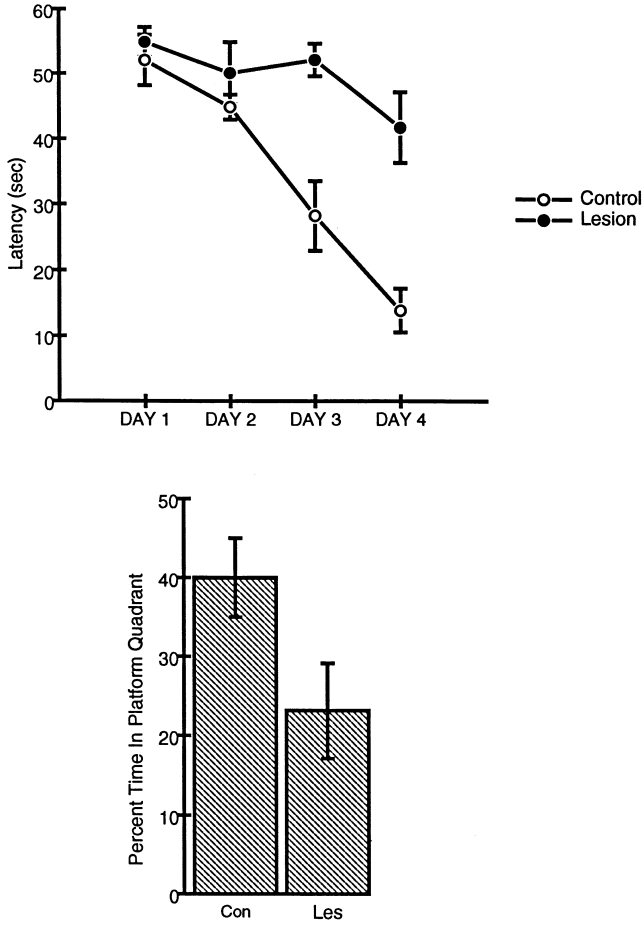

FIG. 4. Effects of photothrombotic bregma-level lesions on acquisition of the water maze (n = 8). Top panel: Latency to find platform (mean ± SEM of each rat's trials blocked across day). Bottom panel: Percent time spent in platform quadrant during probe trial (mean ± SEM).

Four days after surgery, the rats were trained in the water maze as described above.

The lesion-induced impairment of performance was not attenuated by flunarizine (Fig. 3). Analysis of variance revealed a significant effect of treatment on the latency to find the platform [Groups, $F(2, 18) = 3.60$, $p = 0.049$]. Multicomparisons of the data indicated that there was no significant difference between the lesion and flunarizine groups. There was also a significant effect of day [Day, $F(3, 54) = 20.90$, $p < 0.001$] and a significant interaction between treatment and day [Groups × Day, $F(6, 54) = 2.57$, $p = 0.03$]. Percent time spent in the platform quadrant during the probe trial was also significantly decreased in the lesion group, and this was not attenuated by flunarizine (Fig. 3). Analysis of variance indicated that there was a significant treatment effect [Group, $F(2, 17) = 17.96$, $p < 0.001$]. Multicomparison of the data indicated that there was no significant difference between the lesion and flunarizine groups.

Water Maze Acquisition: Effect of Bregma-Level Lesion

Sixteen rats received either sham (n = 8) or rose bengal (n = 8) bregma-level lesions, and 4 days after surgery the rats were trained in the water maze as described above. Acquisition of the platform position in the water maze task was significantly impaired in the lesion group (Fig. 4). Analysis of variance revealed a significant treatment effect on the latency to find the platform [Groups, $F(1, 14) = 18.47$, $p < 0.001$]. There was also a significant effect of day [Day, $F(3, 42) = 22.20$, $p < 0.001$] and a significant interaction between treatment and day [Groups × Day, $F(3, 42) = 8.30$, $p < 0.001$]. This impairment of learning was further indicated by the percent time spent in the platform quadrant during the probe trial (Fig. 4). There was a significant difference between the control and lesion groups [t_{15} 2.17, $p = 0.048$]. During the first training trial, there was no significant difference in the swim speed between the control (23.8 ± 1.45 cm/s) and the lesion (20.3 ± 2.4 cm/s) groups.

Water Maze Acquisition: Effect of Bregma-Level Lesion with Modified Platform

The previous experiment was repeated with the modified (15 cm with ribbed surface) platform. Sixteen rats received either sham (n = 8) or rose bengal (n = 8) lesions, and 4

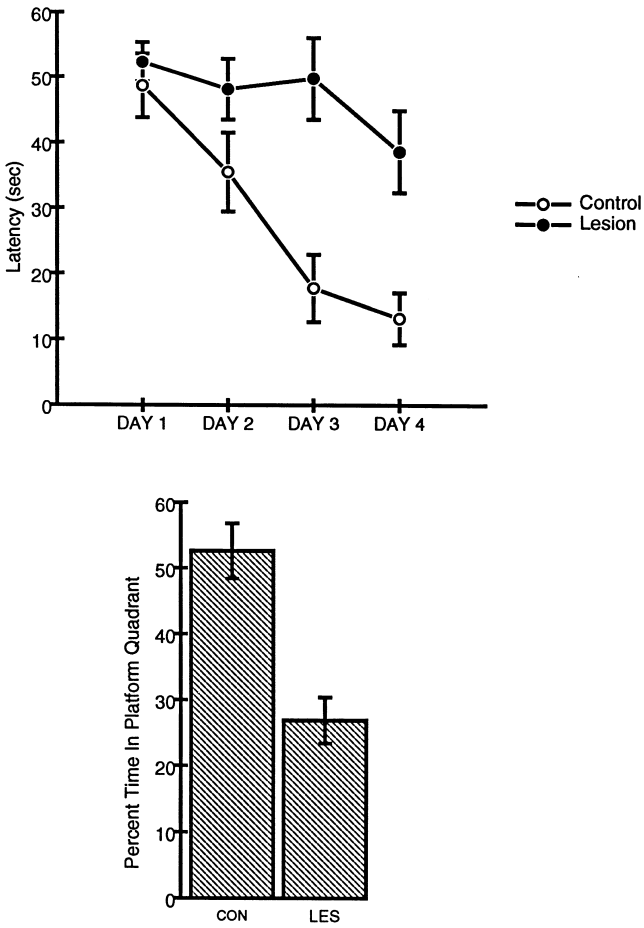

FIG. 5. Effects of photothrombotic bregma-level lesions on acquisition of the water maze with modified platform ($n = 8$). Top panel: Latency to find platform (mean ± SEM of each rat's trials blocked across day). Bottom panel: Percent time spent in platform quadrant during probe trial (mean ± SEM).

days after surgery the rats were trained in the water maze as described above. Acquisition of the platform position in the water maze task was significantly impaired in the lesion group (Fig. 5). Analysis of variance revealed a significant effect of treatment on the latency to find the platform [Groups, $F(1, 14) = 9.35$, $p = 0.009$]. There was also a significant effect of day [Day, $F(3, 42) = 20.33$, $p < 0.001$] and a significant interaction between treatment and day [Groups × Day, $F(3, 42) = 7.33$, $p < 0.001$]. This impairment of learning was further indicated by the percent time spent in the platform quadrant during the probe trial (Fig. 5). There was a significant difference between the control and lesion groups ($t_{15} = 4.69$, $p < 0.001$).

DISCUSSION

In the present study, photothrombotic lesions of the frontal cortex produced pronounced learning and memory deficits in rats, as measured by their severely impaired performance in the water maze spatial learning task. This is in agreement with previously reported studies, which have demonstrated that photochemical thrombosis induced spatial learning deficits (17,29) and impaired performance of operant procedures (6,27). The water maze deficits were of similar severity in both of the lesion positions. Although the lesion positions used in this study were distinct, there was considerable overlap in the nature of damage to specific cortical areas, and we were not able to dissociate the different lesions by their functional effects.

Damage to the frontal or parietal cortex has been associated with a variety of spatial disturbances in humans, although the precise role of the neocortical areas in spatial orientation has not been elucidated. The Morris water maze task has been developed to measure spatial learning in the rat (21,22) and has been used to demonstrate deficits in spatial localisation following lesions of the frontal cortex, although rats with parietal cortex lesions were relatively unimpaired (19). The precise role of different cortical areas in the rat in the performance of spatial tasks is still a matter of some debate, and it has been reported, for example, that prefrontal cortical lesions produce no impairment of learning in the water maze (4). However, there is evidence that frontal and parietal cortical areas are involved in spatial navigation (18). Although there was some damage to motor cortical areas in this study, no obvious gross or nonspecific motor effects were observed. For example, swim speed was not significantly different in lesioned animals compared with controls. We have also demonstrated previously that similar lesions do not produce impairments in spontaneous locomotor activity (27). There may have been more subtle motor or sensorimotor disturbances, as we observed during training in this procedure that some of the lesioned animals had difficulty in mounting the submerged platform in the maze. However, when the paradigm was modified with use of a larger, ribbed platform, there was no detectable deficit in lesioned animals and all of the rats were equally able to climb out of the water, yet the dramatic learning impairment was retained.

There have been few reported effects of neuroprotective agents on both lesion volume and functional deficits in this photochemical stroke model. MK-801 and ganglioside treatments have been shown to attenuate parietal cortex lesions and associated spatial learning deficits (17). Other workers, however, have reported that MK-801 did not reduce infarct volume in a rat thrombotic model (35). Flunarizine has been reported to attenuate photothrombotic-induced sensorimotor deficits in rats (7) and to reduce lesion volume in spontaneously hypertensive rats (31). In the present study, however, flunarizine had no effect on the lesions in that it did not ameliorate the functional spatial learning deficit, and subsequent histological analysis indicated that the drug also failed to attenuate the pathological damage. The discrepancy between the lack of effect of flunarizine seen here and that previously reported may be due to differences in time course. In the DeRyck et al. study (7), flunarizine was only neuroprotective at 24 h and had no effect when measured at 21 days, and in the Van Reempts et al. study (31), the animals were killed at 4 h after surgery. In the present study, the behavioural deficits were not recorded until 4 days after surgery, well past the time a positive effect of flunarizine had been observed previously.

In the present photothrombotic lesion study, it was not possible to correlate significantly the learning and memory deficits with lesion volume in the cortex (data not shown). This suggests that infarct volume in these models is not the only determinant of behavioural deficits and may be in part due to remote effects following cerebral infarction; diaschisis has been demonstrated after cortical photothrombosis in the rat (5). Studies with global ischaemia models have reported

that hippocampal CA1 damage either correlates (26,33) or has no correlation (24) with spatial memory deficits. Focal MCAO ischaemia models have generally used motor and sensorimotor behaviours as functional measures, and these have been reported to provide a good correlation with size of the infarct (14). The assessment of functional deficits in drug studies requires a clear understanding of the relationship between histological damage and functional consequences and, as yet, for the majority of ischaemia models this is clearly not the case.

The photothrombotic model has the advantage that both the location and size of the infarct can be strictly controlled. However, the prominent microvascular injury and early opening of the blood–brain barrier are different from those in human cerebral ischaemia (13). The use of this focal lesion to produce cognitive deficits in the absence of motor dysfunction does have distinct advantages over the relatively more invasive global models of ischaemia and may thus have utility in assessment of the therapeutic potential of neuroprotective agents, as well as increasing our understanding of the functional role of the mammalian neocortex.

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