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ACTH(4–9) Analog ORG2766 Treatment 7 Months Delayed Still Improves Morris Maze Performance of Fimbria-Lesioned Rats

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VAN RIJZINGEN, I. M. S., E. VAN DOREMALEN, M. JOSEPHY, W. H. GISPEN AND B. M. SPRUIJT. *ACTH(4–9) analog ORG2766 treatment 7 months delayed still improves Morris maze performance of fimbria-lesioned rats.* PHARMACOL BIOCHEM BEHAV 53(1) 163–169, 1996.—The ACTH(4–9) analog ORG2766 has been known to affect recovery of damaged functions resulting from injury to neural tissue. The peptides efficacy has often been ascribed to a facilitation of existing recovery, and immediate treatment seemed a prerequisite for efficacy. However, various results in other recovery paradigms do not refer to the neurotrophic properties of the peptide, but rather ascribe the effectiveness of ORG2766 to a general change in attention that indirectly affects functional recovery. Such a change in state is theoretically independent of the occurrence of spontaneous recovery, and, thus, treatment would not be required to coincide with recovery immediately after the damage. To see if ORG2766 can influence the recovery of function without the simultaneous occurrence of spontaneous recovery, this study employed a delay of 7 months after the occurrence of a fimbria lesion before ORG2766 was administered. The selective fimbria lesion produced an impairment in Morris maze performance, which could be attenuated by chronic treatment with ORG2766 immediately after the lesion as well as after 7 months. With respect to spatial orientation, no improvement is assessed in untreated lesioned rats, as the impairment of Morris maze performance in untreated fimbria-lesioned rats is as severe as right after the lesion. The data indicates that efficacy of the ACTH(4–9) analog does not rely on the acceleration of spontaneous recovery processes in this paradigm. The behavioral effects of ORG2766 are discussed in the context of a peptide-induced state of enhanced attention.

ACTH(4–9) analog ORG2766 Fimbria lesion Morris maze Functional recovery Attention Brain damage

ADRENOCORTICOTROPHIC hormone (ACTH) and related peptides can affect functional recovery after damage to the peripheral and central nervous system (11,19,27,28, 30,33,37,38). Administration of the ACTH(4–9) analog ORG2766 after a crush lesion to the sciatic nerve in the hindlimb of the rat accelerates the recovery of sensorimotor impairments. The peptide accelerated collateral sprouting, increased nerve conduction velocity, and improved the pattern of motor unit organization (3,10,12,30,38). In the treated outgrowing fibers an enhanced expression of the growth-associated protein B-50 was demonstrated (40), which suggests a direct involvement of the peptide in renewed outgrowth of damaged peripheral neurons.

After damage to the brain, some studies using 6-OHDA lesions to the nucleus accumbens, the corpus striatum, and the substantia nigra have demonstrated a similar effect of ORG2766 (1,41–44): it accelerated normally occurring recovery through denervation supersensitivity and it increased the number of regenerating DA fibers. Immediate treatment seemed a prerequisite for the occurrence of any peptide efficacy. These effects in the PNS and CNS have collectively been characterized as neurotrophic (18,38,43). There are, however, several studies that do not measure such structural aspects of brain damage; instead, they concentrate on behavioral changes after brain lesions. The recovery of behavioral consequences of lesions to the N. parafascicularis (25), the septum (21), the bulbus olfactorius (Van Rijzingen, in press), and the fimbria-fornix (24,28,33) was improved after peptide treatment. Unfortunately, treatment with ORG2766 is not always beneficial; after a posterior parietal cortex lesion (23) or a

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hippocampus lesion (19) the treatment caused an aggravation of the lesion-induced behavioral impairments, while in some reports on lesions of the neocortex (19), the occipital cortex (32), and the prefrontal cortex (9) treatment was ineffective. Nevertheless, in none of these studies is it clear whether the efficacy of ORG2766 could rely on the aforementioned neurotrophic mechanisms. Actually, some results cannot be easily explained by an assumed neurotrophic efficacy: e.g., the reduction by ORG2766 of the enhanced emotional reactivity after septal lesions (21), or the acute effects on learning and memory that can be assessed directly after administration of the peptide [see (13)]. In these latter studies, in clinical trials and in some of the lesion studies the efficacy of peptide treatment has been interpreted in terms of enhancing the state of attention (4,13,23,31).

Theoretically, such an altered general state may affect the functioning of the damaged brain in the absence of spontaneous recovery. To establish whether peptide treatment may be effective in a recovery paradigm without simultaneously occurring spontaneous recovery, the present study was designed. In previous studies, it has been established that the peptide attenuated the impaired performance of fimbria-fornix-lesioned rats when it was administered immediately after the lesion. Morphological studies by Gage et al. (14,15) demonstrated that a fimbria-fornix lesion is followed by a reinnervation of the hippocampus by means of the the entorhinal path. After 6 months acetylcholine, serotonin, and noradrenaline staining was present again in the denervated hippocampus. In the present study, a time interval of 7 months between lesion and treatment was applied to assure that treatment and spontaneous recovery do not coincide. A prerequisite for this question is an impaired performance after 7 months, which was, indeed, assessed in this study. In addition, the animals received a specific fimbria lesion instead of the previously used fimbria-fornix lesion, in order refine the experiment. It appears that the fimbria fornix cannot be seen as a single functional unit. The fimbria and fornix fibers are distinctive in origin, target area, and some behavioral aspects (6); for instance, in passive avoidance learning. The fimbria lesion has been chosen because in a study on acquisition of a complex spatial discrimination task (39) both a selective fimbria lesion and a combined fimbria-fornix lesion were seen to affect learning.

METHOD

Animals

Male Wistar rats (R.M.I livestock, Utrecht), approximately 2 months of age, were group housed (three rats per cage) in makrolon cages (type 3) with sawdust bedding and ad lib rat chow and water. Day-night cycle was reversed (low red light from 0800–2000 h).

Surgery

Fimbria lesion. The rats (±200 g) were anesthetized with an intramuscular injection of Hypnorm (Duphar, Weesp, NL), which contains flunisone (10 mg/ml) and pentanylcitrate (0.2 mg/ml) prior to surgery. The head was fixed in a stereotactic apparatus. The nose clip was elevated +4.0 mm, resulting in a slope of the skull of 30°C. Two grooves were drilled in the skull, the first with the position of 0.5 mm anterior, +3.0 mm lateral from bregma to 1.0 mm posterior, +1.5 mm lateral to bregma, and the second with the position of 0.5 mm anterior, −3.0 mm lateral from bregma to 1.0 mm posterior, −1.5 mm lateral to bregma [adapted from (26)]. The transection was made with a specially designed knife, 1.2 mm wide, 5.5 mm deep, and placed from caudo-medial to rostro-lateral at a depth of 5.5 mm below the skull surface. The fimbria is bilaterally transected during this procedure: the fornix remains intact (see Fig. 1). (Sham operations consisted of skin incising and drilling of the skull; the cortex was not damaged.)

Morris Maze

A Morris maze apparatus was used with a black pool (diameter 200 cm, depth 40 cm), which was filled with water (temperature 27 ± 1°C). Low red light conditions resulted in a black water surface under which the black platform could not be detected. In quadrant 1 of four fixed quadrants a black escape platform was placed 1 cm below the surface, the visible platform was white, and extended 1 cm above the surface. Cues were provided by two white boards with black signs placed around the rim of the pool. Observations were made using an automated system described below. All rats received 16 trials during acquisition training, 4 trials each day on 4 consecutive days, with an intertrial interval of 10 min. A rat was entered facing the wall at random on one of four entry points, and allowed to swim for 120 s. The latency until the rat mounted the platform was recorded. If the rat failed to find the platform within 120 s it was guided there by hand (latency was set at 120 s) and allowed to remain on the platform for 30 s. On the fifth day, the platform was removed.

FIG. 1. Location of the bilateral fimbria lesion indicated by ▲. This transversal coupe was specially made for the visualization of the location of the lesion. It was stained with a standard thionine staining.

All rats entered at a fixed point and allowed 60 s to swim, during which their swimming pattern was recorded by the automated system. During analysis, the time and travelled distance in four zones was measured: the pool was divided into four equal quarters; the previous location of the platform was in the center of quadrant 1.

Automated System

A video camera, mounted above the center of the pool, was directly connected to a computerised image analysis system that records the rats position approximately twice per second. After defining zones in the recorded field, the time and travelled distance per zone and the latency to enter each zone can be calculated by the program. Hardware consisted of an IBM AT computer, combined with a PC vision frame grabber (Imaging Technology Inc., USA) and a CDD video camera. The software was developed by Noldus Information Technology, Wageningen, The Netherlands (35).

Histology

After testing, the animals were sacrificed, the brains were carefully removed, and dissected wet. The cortex was folded back. The fimbria is then visible as a white cable attached to the hippocampus. It was visually inspected whether the cable was completely transected and whether the hippocampus was undamaged.

Statistical Analysis

In Experiment 1, the latency to reach the platform during acquisition was tested with a two-way analysis of variance (ANOVA) on the factors surgery (fimbria lesion vs. sham lesion) and platform (visible vs. invisible) with repeated measurements (16 trials). The probe trial was analyzed by a two-way ANOVA on the factors surgery and platform to detect differences in the time spent in the previously reinforced quadrant.

In Experiment 2, the latency times during acquisition were tested using a three-way ANOVA on the factors surgery (fimbria lesion vs. sham lesion), treatment (ORG2766 vs. saline) and time of treatment (immediate vs. delayed) with repeated measurements (16 trials) to detect if differences in escape latency were dependent on each of these factors. The probe trial was analyzed with a three-way ANOVA on the factors surgery, treatment, and time of treatment.

Procedure, experiment 1. Thirty-three male wistar rats were given sham or fimbria lesions and received a series of seven subcutaneous injections, one injection every 48 h (called chronic treatment) with saline (0.5 ml) for 2 weeks prior to behavioral testing. Morris maze testing began on day 16 after the lesion. (The rats tested with the invisible platform were groups equal to the ones in Experiment 2.)

Procedure, experiment 2. Sixty-four male wistar rats were divided over two experiments: the experimental groups were given Morris water maze testing either 2 weeks or 7 months after fimbria lesioning. All animals (sham and fimbria-lesioned) received a series of seven subcutaneous injections, one injection every 48 h, with either saline (0.5 ml) or ORG2766 (1 μg/0.5 ml) in the 2 weeks prior to testing. Morris maze testing began either 16 days after the lesion (48 h after the last injection), or 7 months + 2 weeks after the lesion (also 48 h after the last injection).

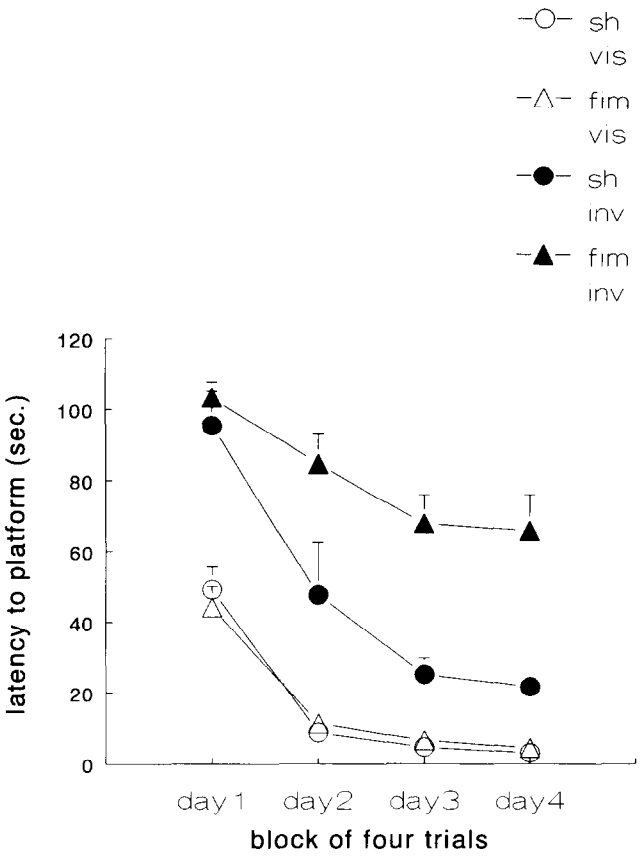

FIG. 2. Mean latencies (in s ± SEM) to reach the platform in the Morris maze for each group per day. Each day depicts a mean of four trials. Vis = rats were tested with the visible platform; Inv. = rats were tested with the invisible platform; Sh = sham lesion; Fim = fimbria lesion. Group sizes were: sh/vis n = 7, sh/inv n = 8, fim/vis n = 8, fim/inv n = 9.

RESULTS

Experiment 1

In the first test, the effect of a fimbria lesion on the Morris water maze performance was investigated. For dissociating visual-motor coordination and spatial learning the performance of lesioned rats with a visible and an invisible platform have been compared. The escape latency (Fig. 2 depicts blocks of four trials) declines in the 4 days of testing. In the task with the visible platform, animals reached the platform significantly faster than in the task with the invisible platform [within subjects: platform effect $F(1, 27) = 95.74$ $p < 0.001$]. Performance rates with the visible platform did not differ between lesioned and unlesioned rats, which indicates no locomotor deficit or motivational decline resulting from the lesion. In the task with the invisible platform, fimbria-lesioned rats were clearly impaired when compared to sham rats [within subjects: surgery effect, $F(1, 27) = 11.75$ $p < 0.002$, surgery × platform effect, $F(1, 27) = 11.43$ $p < 0.002$]. This suggests that the fimbria is specifically involved the cognitive aspects of the spatial orientation task.

The data of the probe trial (Fig. 3) show that both groups trained with the visible platform did not swim more in the

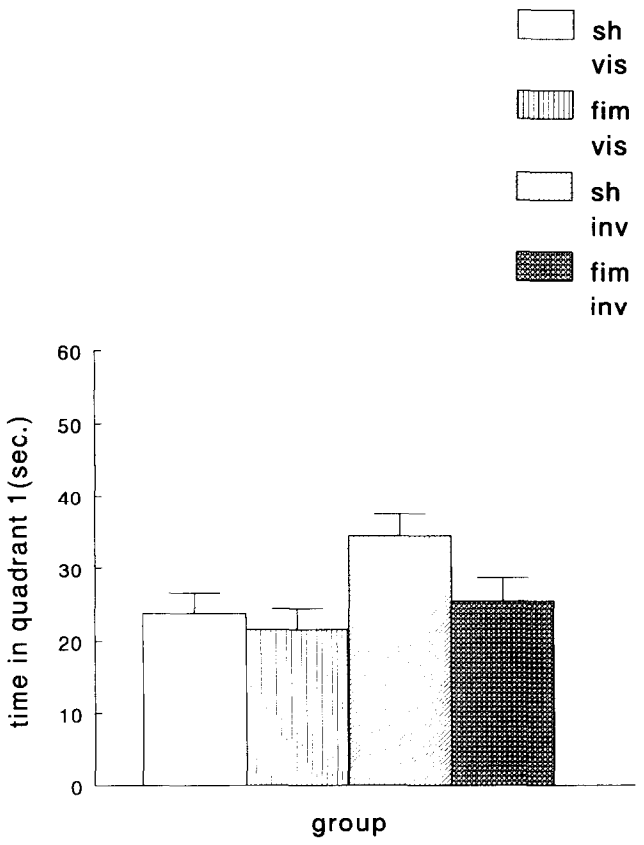

FIG. 3. Mean time spent in quadrant 1 in the Morris maze (in s ± SEM) for each group during the trial without platform. Quadrant 1 held the platform during acquisition trials. sh = sham lesion; fim = fimbria lesion; sal = saline treatment; org = ORG2766 treatment. Groups as in Fig. 2.

previously reinforced quadrant than in one of the other quadrants. The sham-operated rats tested with the invisible platform spend more time in quadrant 1, which indicates that they use spatial orientation in this task. Fimbria-lesioned rats did not persist in swimming in the previously reinforced quadrant [within subjects, surgery effect, $F(1, 27) = 10.1, p < 0.003$], which demonstrates a deficit in spatial orientation resulting from the lesion.

Experiment 2

This series of experiments investigated an influence of the ACTH(4–9) analog on the fimbria lesion-induced impairment in the Morris maze, the peptide was administered either immediately after surgery or after a 7-month delay. For clarity, the data is presented in two separate graphs, one depicting latency to reach platform for the immediately treated groups, one for the groups that received delayed treatment. Statistical analysis, however, has been performed over the combined dataset to enable a triple-factorial test. Preliminary testing of the control groups (sham saline immediate vs. sham saline delayed) demonstrated no significant difference, which justifies collective testing in a three-way analysis of variance. The escape latency during acquisition of the test (Figs. 4 and 5) was higher for lesioned rats than for sham-operated rats [within subjects: lesion effect, $F(1, 55) = 37.673, p < 0.001$], but there was also an interaction effect of lesion × time of treatment [within subjects: $F(1, 55) = 7.222, p < 0.010$], sham groups had a higher latency after 7 months of independent of treatment. This effect could perhaps be ascribed to the greater age of the animals.

Within each group the latency times declined over 16 trials, which indicates that the task was learned correctly in the course of the 4 days [between subjects: time effect, $F(3, 165) = 86.503, p < 0.001$]. There was an interaction time × surgery; latencies declined at a slower rate for fimbria-lesioned groups than for sham groups; thus, sham groups learned the task faster than fimbria-lesioned groups [between subjects: surgery × time, $F(3, 165) = 3.577, p < 0.015$]. Most importantly, there was an interaction between time, surgery, and treatment; latency times decline faster for treated lesioned rats than for untreated lesioned rats. Treatment did not affect sham-operated rats. The treatment specifically affected lesioned animals [between subjects: surgery × time × treatment, $F(3, 165) = 3.684\ p < 0.013$]. There was no interaction with the time of administration, which shows that the effect is independent from any delay.

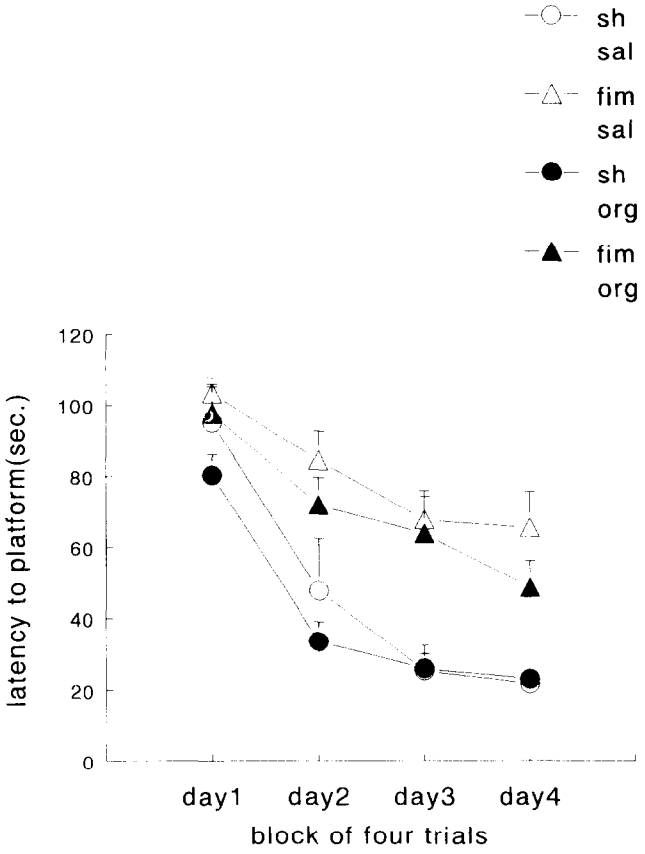

FIG. 4. Mean latencies (in s ± SEM) to reach the platform in the Morris maze for each group per day. Each day depicts a mean of four trials. ORG2766 treatment (10 μg/rat/48 h for 14 days) was given immediately after the lesion. Sh = sham lesion; fim = fimbria lesion; sal = saline treatment; org = ORG2766 treatment. Group sizes were: sh/sal $n = 8$, sh/org $n = 8$ fim/sal $n = 9$, fim/org $n = 8$.

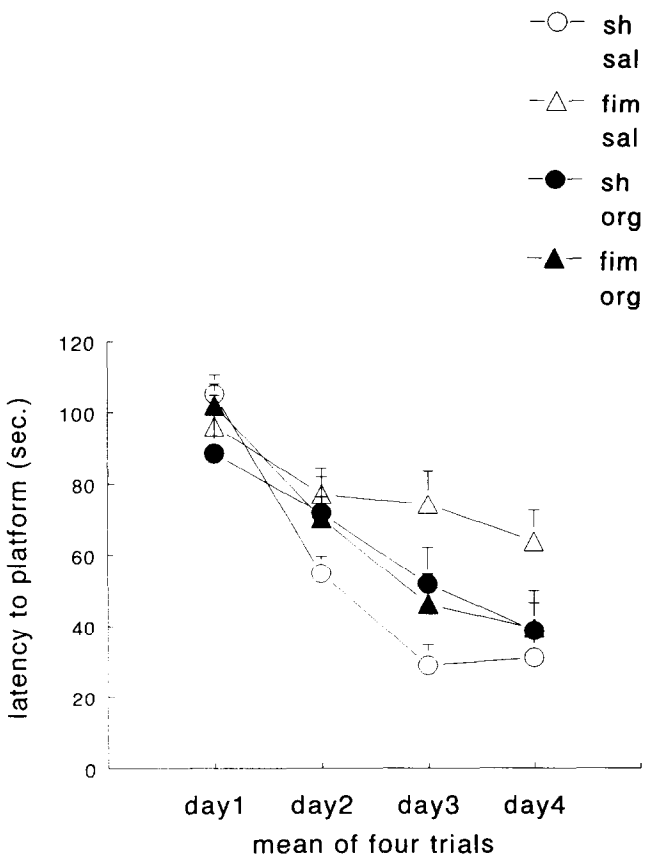

FIG. 5. Mean latencies (in s ± SEM) to reach the platform in the Morris maze for each group per day. Each day depicts a mean of four trials. ORG2766 treatment (10 μg/rat/48 h for 14 days) was given 7 months after the lesion. Sh = sham lesion; fim = fimbria lesion; sal = saline treatment; org = ORG2766 treatment. Group sizes were sh/sal n = 7, sh/org n = 7, fim/sal n = 8, fim/org n = 8.

Analysis of the probe trial data (Fig. 6) shows a lack of persistence to search for the platform only in saline-treated fimbria-lesioned rats: they spend significantly less time in the previously reinforced quadrant [surgery effect, $F(1, 55) = 4.214$, $p < 0.043$]. This impairment was equally present after 7 months, which confirms that no spontaneous functional recovery has occurred. The peptide ORG2766 had an overall facilitating effect [treatment effect, $F(1, 55) = 5.918$ $p < 0.017$], though there is a trend that this facilitation was more profound in fimbria-lesioned rats. [Interaction treatment × surgery, $F(1, 55) = 3.645$, $p < 0.060$]. This effect was again independent of the delay.

DISCUSSION

Spatial orientation is clearly impaired in rats with a selective fimbria lesion, while no effects on sensorimotor control could be established. These findings appear to be consistent with results obtained in previous studies after a combined fimbria-fornix lesion (27,28,33); thus, the behavioral effects are attributed (at least partly but probably primarily) to the fimbria fibers from the hippocampus to the septum.

The deficit in Morris maze performance is present both 2 weeks and 7 months after the lesion. Gage et al. (14,15) reported that in 6 months acetylcholine, serotonine, and noradrenaline staining are present again in the hippocampus after a fimbria-fornix lesion as a consequence of reinnervation via the entorhinal path, but the results of the present study indicate that this does not result in actual behavioral recovery of impaired performance in the Morris maze. Administration of the ACTH(4-9) analog ORG2766 is capable of reducing these impairments, even when the administration is postponed for 7 months. Thus, it appears that ORG2766 can attenuate permanent behavioral consequences of brain damage in the absence of spontaneous behavioral recovery. The efficacy of the peptide cannot be ascribed in this paradigm to an influence on short-term mechanisms like denervation supersensitivity, nor to restored innervation; therefore, a neurotrophic effect of the peptide seems highly unlikely.

A different explanation for the influence of the ACTH(4-9) analog is proposed in a study on recovery after labyrinthectomy (20) in squirrel monkeys. It was suggested that the undamaged contralateral brain structure compensated for the loss of functioning, thus accounting for the enhanced func-

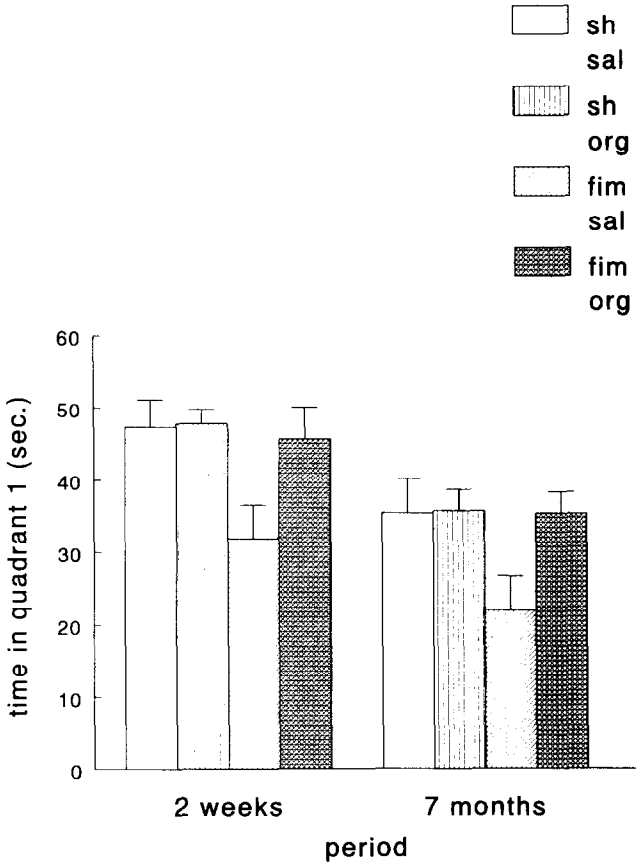

FIG. 6. Mean time spent in quadrant 1 in the Morris maze (in s ± SEM) for each group during the trial without platform. Quadrant 1 held the platform during acquisition trials. 2 weeks = treatment immediately after the lesion; Morris maze testing 2 weeks after the lesion; 7 months = treatment 7 months delayed; Morris maze testing began immediately after the treatment schedule was finished; sh = sham lesion; fim = fimbria lesion; sal = saline treatment; org = ORG2766 treatment. Groups as in Figs. 4 and 5.

tional recovery. Because the fimbria lesion used in this study was bilateral, contralateral compensation seems an improbable explanation of the present results. However, it could still be possible that other undamaged brain structures have partly taken over the lost functions.

The early studies on the efficacy of acute peptide treatment in learning and memory paradigms and the results of various clinical trial forwarded the hypothesis that ACTH-like neuropeptides improve the attention to all external stimuli irrespective of their relevance (enhanced nonselectivity), and increase sustained attention (4,13,23,31). Chronic treatment is assumed to mimic acute treatment, but the resulting state of enhanced attention endures longer. Such a long-lasting enhancement of attention to environmental stimuli may be able to account for the return of lost functions found both in the present study and several other lesion studies: a) it has been shown (22) that providing abundant cues could counteract the radial maze performance impairments found in hippocampal system damaged rats. In a spatial orientation task an elevated attention to (and heightened processing of) a few cues could, likewise, make the task easier to learn. b) Administration of ORG2766 to cortical-lesioned rats increased the number of errors made in a T-maze. The authors suggested that the treated rats were distracted by irrelevant stimuli (23). An enhancement of nonselective attention for the distracting stimuli resulting from peptide treatment might cause the magnification of the deficit. c) Hippocampal-damaged rats show attentional deficiencies in a holeboard task (19), which are attenuated by ORG2766. d) In aged animals the reported long-lasting effects of chronic treatment on social behavior (34) may also be explained by increased attention.

The beneficial effect of a general brain state of enhanced attention should be present at any time after the brain damage, while the peptide-induced acceleration of spontaneous recovery requires that administration coincides with the time course of this mechanism.

Any attempt to conceptualize about the mechanism(s) of action of the peptide is, however, hampered by the fact that the physiological substrate of ORG2766 is as yet unclear. Three of the five melanocortin receptors are localized in the brain; MC3, MC4, and MC5 (7,16,29), and even though larger ACTH/MSH fragments readily activate these receptors, smaller fragments, and ORG2766 in particular, fail to do so (Adan et al., submitted).

The peptide has been demonstrated to modulate the activity of the NMDA-receptor system: the behavioral effects of injections with NMDA and its antagonist AP5 can be counteracted by ORG2766 treatment (36). ORG2766 itself has no direct agonistic capacity for the NMDA receptor, as evidenced by the fact that in the same paradigms where NMDA and AP5 were seen to evoke behavioral responses, the peptide alone did not have any effects. Modulation of NMDA receptor system activity can have neuroprotective consequences (2), as discussed extensively in (36). Furthermore, the NMDA receptor system is associated with recovery of behavioral malfunctioning after unilabyrinthectomy. The spontaneous recovery process (known as vestibular compensation) could be disrupted through administration of the NMDA receptor antagonist CPP (17). Pretreatment with ORG2766 prevented this disruption, which indicates that the beneficial effect of ORG2766 on vestibular compensation also relies on the NMDA receptor system. The NMDA receptor is also essential for long-term potentiation (LTP) (8), which is an increase in synaptic efficacy supposedly underlying learning and memory. The occurrence of LTP is strongly modulated by the state of alertness of the animal (5). Thus, the classic effects of ORG2766 on learning and memory through enhanced attention could also possibly be due to a modulation of NMDA receptor activity.

However, the hypothesis that a connection between ORG2766 and NMDA receptor system activity would be responsible for functional recovery through enhanced attention and/or accelerated spontaneous recovery is as yet tentative, and not supported by sufficient evidence. Still, the notion that both mechanisms of action of the peptide may rely on a common physiological substrate seems promising enough to instigate further research in this field.

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