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Infusion of D-cycloserine into temporal-hippocampal areas and restoration of mnemonic function in rats with disrupted glutamatergic temporal systems

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Abstract

Partial transections of the fiber connections between the temporal cortex and the lateral entorhinal cortex at a site of the white matter corresponding to the perirhinal cortex result in impaired visual memory accompanied by reduced concentrations of glutamate in both the temporal cortex and lateral entorhinal cortex. Intraperitoneal administration of the glycinergic receptor agonist D-cycloserine produces complete restoration of memory function, as measured by a brightness discrimination task in rats with temporal cortex/lateral entorhinal cortex transections. The purpose of the present study was to identify in which brain structures the compensatory activity might take place. The results show that infusion of cycloserine into either the temporal cortex or lateral entorhinal cortex fully ameliorated the impairment of temporal cortex/lateral entorhinal cortex lesions, whereas infusion into the hippocampal region caused only a mild improvement of the retention performance. Infusion of cycloserine into the frontal cortex or saline into the temporal cortex or lateral entorhinal cortex had no ameliorating effects on the memory dysfunction of rats bearing temporal cortex/lateral entorhinal cortex transections. It is concluded that the temporal cortex, lateral entorhinal cortex and perirhinal cortex are highly critical in forming visual memory.

Keywords: Memory impairment; (Microinjection); D-Cycloserine; Temporal cortex; Entorhinal cortex; Recovery of function

1. Introduction

A growing body of evidence indicates that the temporal-entorhinal complex is critically involved in mnemonic functions. In the rat, lesions of the perirhinal cortex, which mediates connections between the temporal and entorhinal cortices, result in impairment of long-term and short-term preservation of sensory information (Mumby and Pinel, 1994; Myhrer and Wangen, 1996; Nagahara et al., 1995; Otto and Eichenbaum, 1992; Wiig and Bilkey, 1994a,b). The hippocampal region (hippocampus proper, fascia dentata and subiculum), however, appears to contribute more to temporary storing of information than its long-term preservation (Jarrard, 1993; Rawlins, 1985).

The hippocampal region receives sensory information from neocortical association areas by way of the perirhinal and entorhinal cortices. This information is transmitted from the medial and lateral entorhinal cortex via the perforant path projection system to the hippocampal region. In return, the hippocampal region is able to send information to the entire cortical mantle. Furthermore, the lateral entorhinal cortex is heavily connected with the temporal cortex, whereas the connections between the temporal cortex and the medial entorhinal cortex are relatively modest. The fiber connections of the temporal cortex and the lateral entorhinal cortex are routed in the adjacent white matter (cf. Myhrer, 1992).

Transection of the connections between the temporal cortex and the lateral entorhinal cortex causes a more pronounced impairment of retroactive memory (retrograde amnesia) than proactive memory in a visual discrimination task (anterograde amnesia; Myhrer, 1991, 1992). At least some of the disrupted neurons use glutamate as neurotransmitter, because retrograde amnesia in rats with temporal cortex/lateral entorhinal cortex lesions is accompanied by reduced high-affinity D-aspartate uptake in both the temporal cortex and lateral entorhinal cortex (Myhrer et al., 1989). The likelihood that glutamate-mediated neurotransmission is affected by temporal cortex/lateral entorhinal

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cortex transections is corroborated by the finding that administration of glutamatergic agonists can completely restore memory function in rats with temporal cortex/lateral entorhinal cortex lesions. Retroactive memory is fully ameliorated by i.p. injections of NMDA, glycine, or AMPA, whereas administration of kainic acid only produces a slight improvement of memory (Myhrer and Paulsen, 1992). However, systemic application of agonists does not provide information about the localization of the compensatory processes. It might be of clinical value to elucidate which subregions of the brain contribute to the recovery of memory function, because temporal cortex/lateral entorhinal cortex lesions have been suggested to serve as a glutamatergic denervation model of Alzheimer's disease (Myhrer, 1993). Direct infusion of agonists into critical areas may help to clarify the issue of which sites support the recovery processes.

Potent agonists may cause further damage by excitotoxic effects in rats with lesion-induced amnesia. For this reason, the partial glycine receptor agonist D-cycloserine, which modulates the glycine site of the NMDA receptor, has received attention in some recent studies. Cycloserine freely crosses the blood-brain barrier (Monahan et al., 1989) and has about 60% of the maximal response of glycine (Huettner, 1991). This agonist has been shown to be a positive modulator of the glycine site of the NMDA receptor (Monahan et al., 1989) and is able to enhance memory performance in lesioned rats, intact mice and intact rabbits (Flood et al., 1992; Quartermain et al., 1994; Schuster and Schmidt, 1992; Thompson et al., 1992).

We have determined the action profile of cycloserine in rats with temporal cortex/lateral entorhinal cortex transections in a three-choice visual discrimination task used in previous studies. The results show that i.p. injections given shortly after surgery (0–1 days) or just prior to retrieval (12 days after surgery) are much more effective in improving memory than injections given between these extremes (Myhrer and Paulsen, 1995). The purpose of the present study was to investigate the effects of temporal cortex/lateral entorhinal cortex lesions on retroactive visual memory in rats injected with cycloserine (or vehicle) in relevant structures immediately after completion of the lesion surgery. The structures infused were the temporal cortex, lateral entorhinal cortex, hippocampal region, or the frontal cortex. The latter has been shown to be important for memory processing in tasks involving learning of rules (Otto and Eichenbaum, 1992).

2. Materials and methods

2.1. Subjects

Forty-three male Wistar rats from a commercial supplier (Møllegaard Breeding Laboratories, Denmark), weighing 280–310 g at the time of surgery, served as subjects. The experiments were approved by the Norwegian committee for work with laboratory animals. The rats were randomly assigned to five groups, and their group assignment was not known during testing. Ten rats received temporal cortex/lateral entorhinal cortex transections and one injection of cycloserine in the temporal cortex (five rats) or lateral entorhinal cortex (five rats). Eight rats received temporal cortex/lateral entorhinal cortex lesions and one injection of saline in the temporal cortex (four rats) or lateral entorhinal cortex (four rats). Ten rats received temporal cortex/lateral entorhinal cortex transections and two injections of cycloserine (five rats) or one injection of cycloserine in the hippocampal region (five rats). Seven rats received temporal cortex/lateral entorhinal cortex lesions and one injection of cycloserine in the frontal cortex. All lesions and drug infusions were made bilaterally. Eight control animals had their scalp reflected only. The rats were housed individually and had free access to commercial rat pellets and water, except when deprived of water during the testing period. The animals were handled individually 3 days preoperatively and 1 day postoperatively, and were allowed to explore a table top (80×60 cm) for 3 min a day. The climatized (21°C) vivarium was illuminated from 07:00–19:00 h.

2.2. Surgery

The rats were anesthetized i.p. with diazepam (10 mg/kg) and fentanyl fluanisone (2 mg/kg) and placed in a stereotaxic head holder with their skulls horizontal. The bilateral lesions were made mechanically by means of the sharp edges of cannulas (diameter 0.5 mm) provided with a collar to control for insertion depth. The cannula to be used was mounted on a syringe. The point of insertion was 7.8 mm posterior to bregma and 6.7 mm lateral to midline. Each cannula was inserted into the brain in a position deviating 20° from the vertical in the sagittal plane (tip of cannula pointing rostrally). From this position the syringe was moved seven times back and forth in an axis deviating about 45° from the frontal plane (opening of angle pointing medially). These maneuvers were carried out in two stages with insertion depths 6 and 8 mm from top of skull. In this way, the distal part of the angular bundle was transected at a site corresponding approximately to the level of the rhinal fissure.

The site for temporal cortex injections was 4.0 mm posterior to bregma and 6.0 mm lateral to midline. The cannula (diameter 0.8 mm) was inserted 6.0 mm from the top of the skull in an angle of 15° with the tip of cannula pointing laterally. The point of insertion for lateral entorhinal cortex injections was 7.8 mm posterior to bregma and 6.0 mm lateral to midline. The cannula was inserted 8.0 mm from the top of the skull in an angle of 10° with the tip of cannula pointing laterally. The double insertions in the hippocampal region were made 3.5 mm posterior to bregma, 2.0 mm lateral to midline (insertion I), and 5.0

mm posterior to bregma, 4.0 mm lateral to midline (insertion II). In insertion I, the cannula was lowered perpendicularly 3.5 mm and in insertion II 4.8 mm. The single insertion in the hippocampal region was made 4.2 mm posterior to bregma, 3.0 mm lateral to midline with depth 3.5 mm from the top of the skull. The insertion site for frontal cortex was 3.5 mm anterior to bregma, 2.5 mm lateral to midline, and depth 4.0 mm from the top of the skull. The infusions were made by means of a microinjection pump (Model CMA 100, Carnegie Medicin, Stockholm, Sweden).

2.3. Histology

Upon termination of testing, the animals were placed in the stereotaxic head holder under anesthesia. Then 1.0 μl of 4% methylene blue in saline was infused during 1 min (and the cannula remained in position for 1 min extra) with the same co-ordinates as previously used to mark the position of cannula insertions. The animals were decapitated, and the brains were removed and frozen. The brains were sectioned horizontally on a CO_2-freezing microtome at 30 μm, every 12th section being preserved. The sections were stained with methylene blue after they had been inspected for location of cannula marks. The extent of fibers transected was estimated from the degree to which the white matter between temporal cortex and lateral entorhinal cortex was damaged at the three dorsoventral levels presented in Fig. 1. The white matter (not the alveus) was divided into four equal columns, each column representing 25% of the fibers. The occurrence of damage was evaluated under ×75 magnification. The number of columns affected at each dorsoventral level was counted, and the mean percentage of damage was computed for each animal.

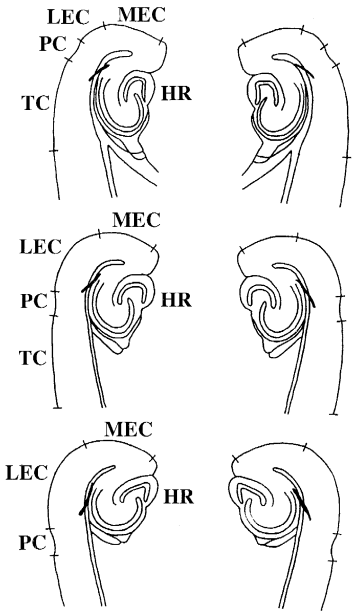

Fig. 1. Reconstruction of horizontal sections indicating location of a typical example of temporal cortex/lateral entorhinal cortex transections representative for all groups. Distance between sections: 1.5 mm.

2.4. Drugs

D-Cycloserine (Sigma) was dissolved in 0.9% physiological saline. The dose was 1.0 μl (1.0 μg/μl) applied for 1 min, and the cannula remained in position for an additional 1 min before retraction. This procedure was based on the results from a pilot experiment. Physiological saline (1.0 μl) was infused in the same manner.

2.5. Apparatus

Testing of simultaneous brightness discrimination was carried out in a Plexiglas cage (56 × 34 × 20 cm) previously described (Myhrer and Nævdal, 1989). In brief, a Plexiglas wall with an opening (10 × 10 cm) in the middle divided the apparatus into two equal compartments: the start compartment and the goal compartment. Three interchangeable aluminum cylinders (3 × 7 cm) with a round well (2 × 2 cm) in the top served as discriminanda. The cylinders were located in fixed positions (equal distance between each) along the wall opposite to the partition wall in the goal compartment. The cylinders were natural grey (aluminum) or painted black (except for the well). The well of the positive cylinder was filled with water. The only light was a 15-W bulb 60 cm above the apparatus.

2.6. Procedure

During acquisition and retention testing the rats were deprived of water for 23.5 h a day. Prior to acquisition, each rat was allowed to explore the empty test apparatus for 15 min. On the first day of acquisition, the subjects were trained to discriminate between the cylinders and received some laps of water from the well in the positive cylinder. That is, the rats were permitted to inspect cylinders until they encountered the correct one. They were given ten trials, the intertrial interval was 20 s during which the rats stayed in their home cage. On the second day, the animals were given trials until there were five correct responses in succession. Because the task is rapidly learned, the learning criterion was set low to avoid overlearning.

The rats underwent surgery 24 h after the learning criterion had been achieved. Twelve days following surgery, the animals were tested for retention of the discrimination task. Testing was terminated when the previous criterion was reached. The following behaviors were recorded: number of trials needed to attain criterion performance, number and type of errors before criterion performance was reached. In order to drink or investigate whether the well in a cylinder contained water the rats had to stand

on their hind legs with at least one forepaw on top of the cylinder. Error response was scored when a negative cylinder was mounted and found empty of water (e.g. licking the empty well). Approaching or investigating negative cylinders (except the well) was not scored as an error. The positive cylinder was either black or grey and the two cylinders of opposite color were negative. The position of the positive cylinder (left, middle, right) was changed in a prearranged randomized order. One set of randomized positions was used on the first day of training and another one on the second day and on retention testing. A counterbalanced paradigm was followed in which half of the subjects were trained with the black cylinder as positive and the other half with the grey cylinder as positive.

During the initial phase of learning this task, rats frequently put their snouts close to negative cylinders and then left the cylinders. Because olfactory cues are of no guidance in this respect, the rats most likely respond to the color. An approach to a positive cylinder was immediately followed by rearing and drinking from the well. As training proceeded, rats gradually ceased to approach the negative cylinders and headed for the positive cylinder when they entered the goal compartment. It is not likely that rats changed their learning strategy at this stage of training by approaching the positive cylinder because of its odd appearance (one positive versus two negative cylinders), because rats approached negative cylinders now and then.

2.7. Statistics

Overall analyses were made with one-way analysis of variance (ANOVA) and group comparisons with Newman-Keuls post-hoc test. Computations were carried out with the InStat system, a statistical software program (GraphPad Software, CA, USA).

3. Results

3.1. Histology

The temporal cortex/lateral entorhinal cortex lesions appeared as a section through the white matter at a site between the temporal cortex and lateral entorhinal cortex (Fig. 1). The transections, which often affected the alveus of the hippocampal formation, were 0.5–1.0 mm long in rostro-caudal extent and 3–4 mm long in dorso-ventral extent. Because the cannula transections could not follow the exact curvature of the rhinal fissure, the temporal cortex and lateral entorhinal cortex connections between a relatively small area in the caudal end of temporal cortex and in the rostral end of lateral entorhinal cortex were probably not accessible for denervation (in total about one-third of the fibers). The mean percentage of fiber lesion for all groups was 93 (range 85–100), indicating that a total of about 60% of the fibers between the temporal cortex and lateral entorhinal cortex were disconnected (Fig. 1). The mean percentage of fiber lesion was 93 (range 85–100) for the group infused with cycloserine in the temporal cortex or lateral entorhinal cortex, 95 (range 93–98) for the group infused with saline in the temporal cortex or lateral entorhinal cortex, 92 (range 85–98) for the group infused with cycloserine in the hippocampal region, and 90 (range 85–100) for the group infused with cycloserine in the frontal cortex.

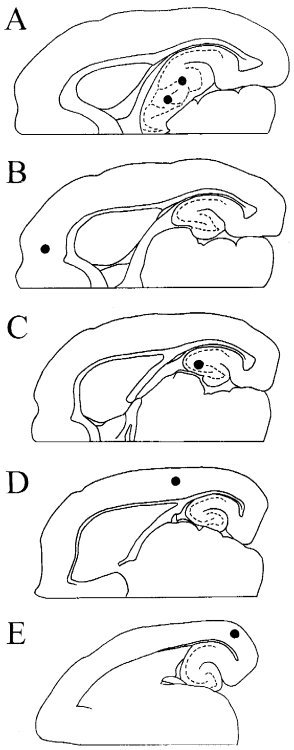

Fig. 2. Reconstruction of horizontal sections showing typical examples of location of infusion cannula: one-site hippocampal region (the most caudal mark in A), two-sites hippocampal region I (the most rostral mark in A) and II (C), frontal cortex (B), temporal cortex (D), and lateral entorhinal cortex (E). The vertical opening of the cannula extended about 1.2 mm above the marks which show the positions of the end of cannula insertions. Distance between sections: A, B, and C: 0.5 mm, C and D: 0.1 mm, and D and E: 2.0 mm.

The localization of representative injection sites is shown in Fig. 2. The dye was found to have spread about 1.0 mm in diameter and was nearly always present in the track made by the cannula insertions. All animals had acceptable cannula placements (i.e. no more than 0.5 mm in deviation from the points shown in Fig. 2). When the infusions were made in the hippocampal region, the dye was often seen to have escaped from the cannula track at a level of the hippocampal alveus and had spread into the lateral ventricle.

3.2. Behavior

The groups from the various treatment categories did not differ significantly in the number of trials required to

Table 1
Mean (±S.E.M.) learning and retention measures for simultaneous brightness discrimination

Lesion	Injection site	Drug	*n*	Acquisition	Retention	
				Trials (total)	Trials	Errors
Sham	–	–	8	17.4 ± 0.63	6.8 ± 0.56	0.9 ± 0.23
TC/LEC	TC or LEC	DCS	10	17.8 ± 0.73	7.4 ± 0.50	1.0 ± 0.15
TC/LEC	TC or LEC	Saline	8	17.6 ± 0.46	21.9 ± 2.35	7.4 ± 1.07
TC/LEC	HR	DCS	10	16.6 ± 0.43	11.8 ± 0.70	3.0 ± 0.21
TC/LEC	FC	DCS	7	16.0 ± 0.58	20.4 ± 1.40	6.9 ± 0.80

Abbreviations: DCS = D-cycloserine; FC = frontal cortex; HR = hippocampal region; LEC = lateral entorhinal cortex; TC = temporal cortex.

reach criterion performance during preoperative acquisition of the discrimination task ($F(4,38) = 1.587$, $P = 0.1976$). During retention, however, rats from the various categories displayed different behavior (Table 1). Whether cycloserine was infused into temporal cortex or lateral entorhinal cortex the results were similar. The number of trials to criterion performance was 7.0 for the temporal cortex and 7.8 for the lateral entorhinal cortex. Also in terms of errors the results were similar (1.0 for both the temporal cortex and lateral entorhinal cortex). Hence, these subgroups were pooled to form a single group. Infusion of cycloserine at one site or two sites in the hippocampal region produced similar results in terms of the number of trials (12.0 for one site and 11.6 for two sites) and errors (3.2 for one site and 2.8 for two sites). For these reasons, the subgroups were pooled. One-way ANOVA confirmed a significant treatment effect for the number of trials to criterion performance ($F(4,38) = 33.190$, $P < 0.0001$). Multiple comparisons with Newman-Keuls post-hoc tests showed that the group which received saline in the temporal cortex or lateral entorhinal cortex and the group that received cycloserine in the frontal cortex consistently needed more trials than the sham group and the group infused with cycloserine in the temporal cortex or lateral entorhinal cortex ($P < 0.001$). The group infused with cycloserine in the hippocampal region needed significantly more trials that the sham group ($P < 0.05$) and the group infused with cycloserine in the temporal cortex or lateral entorhinal cortex ($P < 0.01$). However, the hippocampal region group needed significantly fewer trials than the group infused with saline in the temporal cortex or lateral entorhinal cortex and the group infused with cycloserine in the frontal cortex ($P < 0.001$). ANOVA revealed a reliable overall effect in terms of the number of errors made before criterion performance was reached ($F(4,38) = 30.411$, $P < 0.0001$). Group comparisons showed that the group which received saline in the temporal cortex or lateral entorhinal cortex and the group that received cycloserine in the frontal cortex consistently made more errors than the sham group and the group infused with cycloserine in the temporal cortex or lateral entorhinal cortex ($P < 0.001$). The group infused with cycloserine in the hippocampal region made significantly more errors than the sham group ($P < 0.05$) and the group infused with cycloserine in the temporal cortex or lateral entorhinal cortex ($P < 0.01$). However, the hippocampal region group made consistently fewer errors than the group infused with saline in the temporal cortex or lateral entorhinal cortex and the group infused with cycloserine in the frontal cortex ($P < 0.001$). No other significant differences among the groups were found.

4. Discussion

Temporal cortex/lateral entorhinal cortex transections resulted in marked retrograde amnesia in rats which received saline in the temporal cortex or lateral entorhinal cortex. Conversely, cycloserine infused into the temporal cortex or lateral entorhinal cortex in animals bearing temporal cortex/lateral entorhinal cortex lesions caused a complete restoration of the memory function. Cycloserine injected into the hippocampal region resulted in a moderate improvement of memory, whereas this agonist had no beneficial effect at all when infused into the frontal cortex in rats with temporal cortex/lateral entorhinal cortex transections.

The differential effects of cycloserine infused into various areas of the brain suggest that the temporal cortex and lateral entorhinal cortex are crucially involved in preserving information about the discrimination task. Agonists acting at the glycine site of the NMDA receptor make glutamate receptors respond more effectively to endogenous glutamate. For glycine, this is seen as an increased frequency of channel opening and not as an increased current amplitude (Cotman et al., 1988). Cycloserine may enhance synaptic efficacy in remnant glutamatergic systems to compensate for the disruptive effects of temporal cortex/lateral entorhinal cortex lesions on memory. Glycine sites at the NMDA receptors are normally below the saturation point in the hippocampus of rats (Dalkara et al., 1992). Thus, there is room for modulatory effects of agonists acting at the glycine site.

The present findings imply that the compensatory processes primarily take place in the temporal cortex and lateral entorhinal cortex when intraperitoneal administration of glutamatergic agonists completely restores memory function in animals with temporal cortex/lateral entorhinal

cortex lesions. It cannot be precluded, however, that compensatory glutamatergic activity in other structures as well may support the recovery of function, since infusion of cycloserine into the hippocampal region resulted in a slight improvement in performance. The lack of effect seen when cycloserine was infused into the frontal cortex suggests that this brain structure is not involved in the compensatory processes. Results from previous studies have shown that infusion of antagonists acting at NMDA or AMPA receptors into the entorhinal cortex disrupts memory functions in rats (Ferreira et al., 1992; Izquierdo et al., 1993).

The finding that cycloserine is able to antagonize memory impairment when administered shortly after surgery (12 days before retention) suggests that functional mechanisms rather than pharmacological ones are activated. Temporal cortex/lateral entorhinal cortex transections most likely disrupt memory engrams containing vital information from the discrimination task. Since about one-third of the fiber connections between the temporal cortex and lateral entorhinal cortex remained intact after the lesion, the agonist may have strengthened remnant engrams and thus memory function was sustained. It is possible that cycloserine may affect mechanisms of synaptic plasticity in an LTP-like manner. The effects seen when cycloserine was infused into the temporal cortex or lateral entorhinal cortex were probably not associated with an improved ability to relearn the task, because lesions of the temporal cortex or lateral entorhinal cortex impair retention, but not acquisition of the present discrimination task. However, hippocampal lesions impede acquisition, but not retention (Myhrer, 1991, 1992).

When the hippocampal region is damaged 24 h after acquisition of the present task, hippocampal-lesioned rats display normal performance during retention testing (Myhrer and Nævdal, 1989). This finding seems to indicate that information from the task is stored outside the hippocampus. However, the results from experiments with lesions apparently contrast with the present finding that infusion of cycloserine into the hippocampal region 24 h following acquisition had a beneficial effect on retention performance. There might be several possible explanations for these dissimilarities. The cycloserine infused into the hippocampal region may have spread into the temporal cortex or lateral entorhinal cortex. In the case of one-site hippocampal injection the cannula tip was localized about 2.5 mm from the temporal cortex and 4.0 mm from the lateral entorhinal cortex. Methylene blue injected was seen to invade an area of about 1×1 mm. Even if cycloserine spread more effectively than methylene blue, the diffusion of 1.0 μl was probably not able to affect the temporal cortex. Another possible explanation may be found in enhanced glutamatergic neural activity in the hippocampal region in response to cycloserine. The hippocampal region is well provided with projections to the entorhinal cortices (Van Haeften et al., 1995) so that the lateral entorhinal cortex may be stimulated indirectly by increased hippocampal activity. A third possibility may be activation of hippocampal engrams involved during acquisition of the discrimination task. Even if an intact hippocampal region is not necessary for retention performance, the initial phase of the consolidation process is probably still represented in the hippocampal region 24 h following achievement of the learning criterion. Thus, cycloserine infused into the hippocampal region may provide rats bearing temporal cortex/lateral entorhinal cortex lesions with an enhanced ability to relearn the task. The present results do not differentiate between the possible explanations of indirect entorhinal stimulation and weakly preservation of information or improved relearning of the task. In both cases, a moderate improvement of performance might be expected. One possible way to clarify this issue would be to infuse an antagonist into the lateral entorhinal cortex concomitantly with cycloserine infusion into the hippocampal region, unless the antagonist contributes to reinforce the disruptive effects of the temporal cortex/lateral entorhinal cortex transection or block hippocampal output important for the task.

Damage to the orbital prefrontal cortex (the frontal cortex area infused in the present study) results in impaired learning of the rules that govern odor-guided continuous delayed nonmatching to sample (Otto and Eichenbaum, 1992). The simultaneous brightness discrimination measured in the present task appears to be unrelated to the matching task impaired by the frontal cortex lesions. Thus, the lack of effect observed in rats infused with cycloserine into the frontal cortex is consistent with previous findings. However, transection of the fiber connections between the frontal cortex and the temporal cortex results in a weak impairment of retention in the present task (Myhrer, 1991). This finding may be associated more with disruption of temporal cortex functions than frontal cortex functions, since the frontal cortex was unresponsive to infusion of cycloserine.

When cycloserine is administered intraperitoneally a marked enlargement of the temporal cortex/lateral entorhinal cortex lesion site is seen in the left hemisphere (Myhrer and Paulsen, 1995). This result is probably associated with glutamatergic excitotoxic effects potentiated by cycloserine, because the left lateral entorhinal cortex has been shown to contain a higher concentration of glutamate than the right lateral entorhinal cortex in the rats from our local supplier (Myhrer et al., 1989). Even if cycloserine is a partial agonist and has only about 60% of the maximal response of glycine (Huettner, 1991), the drug may exert excitotoxic effects because it freely crosses the blood-brain barrier (Monahan et al., 1989). In the present study, no signs of excitotoxic reactions to 1.0 μl cycloserine were observed at the injection sites. However, during pilot experimentation it was seen that a dose of 3.0 μl cycloserine caused cell death around the injection site.

The transentorhinal cortex is the earliest structure to show neuropathology in Alzheimer's disease (Braak and

Braak, 1991). An area homologous to this area does not exist in the rat, but the perirhinal cortex seems to be the most relevant structure functionally related to the transentorhinal cortex. The connections between the temporal cortex and the lateral entorhinal cortex are relayed in the perirhinal cortex, and selective lesions of this structure result in similar memory deficits as seen following temporal cortex/lateral entorhinal cortex transections (Myhrer and Wangen, 1996). The perirhinal cortex, however, is not readily accessible for selective infusions of neuromodulatory agents because of its shape, making up portions of the dorsal and ventral banks of the rhinal fissure (Burwell et al., 1995).

In conclusion, this study shows that lesion-induced memory impairment related to glutamate deficiency was fully ameliorated by infusion of cycloserine into the temporal cortex or lateral entorhinal cortex, whereas a partial amelioration was seen after hippocampal infusions. Neither saline infused into the temporal cortex or lateral entorhinal cortex nor injection of cycloserine into the frontal cortex affected the memory dysfunction.

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