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Cholinergic neural transplants into hippocampus restore learning ability in monkeys with fornix transections

R.M. Ridley[1], H.D. Thornley[1], H.F. Baker[1], and A. Fine[2]

[1] Division of Psychiatry, Clinical Research Centre, Harrow, Middlesex HA1 3UJ, UK
[2] Department of Physiology and Biophysics, Faculty of Medicine, Dalhousie University, Halifax, NS B3H 4H7, Canada

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Summary. Monkeys with bilateral transections of the fornix were severely but selectively impaired at learning visuospatial conditional tasks presented in a Wisconsin General Test Apparatus. Bilateral transplantation of cholinergic-rich embryonic basal forebrain tissue into the hippocampus led to complete recovery from this specific learning impairment across a range of task difficulties. Administration of the direct cholinergic agonist pilocarpine to ungrafted animals immediately before testing also reduced this impairment, suggesting that the graft-associated recovery was mediated by acetylcholine release. Transection of the fornix produced a marked loss of acetylcholinesterase (AChE) staining confined to hippocampus and entorhinal cortex relative to controls. In all transplanted animals densely AChE-staining cellular masses were seen bilaterally in temporal lobe structures, with fibre outgrowth into surrounding host tissue.

Key words: Cholinergic neural transplants – Hippocampus – Fornix – Learning – Monkey

Introduction

Embryonic septal neurons transplanted into the hippocampus of fimbria-fornix lesioned rats can survive and form anatomically specific patterns of cholinergic connectivity that resemble normal innervation (Björklund and Stenevi 1977; Björklund et al. 1983). Some recovery of function in maze performance has been reported following such transplantation in fimbria-fornix lesioned rats (Low et al. 1982; Nilsson et al. 1986) and in rats whose cholinergic system has been damaged by persistent alcohol ingestion (Arendt et al. 1988, 1989). Assessment of the potential of cholinergic transplants to restore cognitive abilities in human disease requires the demonstration of restoration of function in complex learning abilities in primates. We report that a severe but specific learning impairment in monkeys, induced by transection of the fornix, can be completely overcome by transplantation of cholinergic-rich embryonic basal forebrain tissue into the hippocampus.

Offprint requests to: R.M. Ridley (address see above)

Methods

Eighteen young adult common marmosets *(Callithrix jacchus)* were tested in a Wisconsin General Test Apparatus on a series of visual discrimination learning tasks. This is the standard apparatus for assessment of cognitive abilities in primates (Harlow 1949; Meyer et al. 1965; Baker and Ridley 1986). By raising and lowering an opaque screen the monkey is presented with a series of discrete trials in which two small junk objects (plastic toys etc.) cover two food wells one of which contains a small piece of bread reward. The monkey may displace only one object in each trial and may retrieve and eat the reward if it displaces the correct object. Approximately 40 trials are presented each day with an inter-trial interval of approximately 15 s. Trials are presented until a predetermined criterion (usually 27 correct responses in 30 consecutive trials) is achieved.

Monkeys were tested on two types of task: 1) In visual object discrimination tasks the monkey had to learn to choose one of two different objects in order to obtain food reward. These tasks used multicoloured junk objects (VIS.DIS.) or black junk objects (VIS.DIS.BLACK). Black objects are more difficult for the animals to discriminate (Ridley et al. 1986). 2) In visuospatial discrimination tasks (VIS.SPAT.) the monkey had to choose the object on the left in trials in which one pair of identical junk objects was presented and the object on the right on trials in which an alternative pair of identical objects was presented. The left/right position of the rewarded object in the VIS.DIS. and VIS.DIS.BLACK tasks and the order of presentation of the pairs of stimuli in the VIS.SPAT. tasks (and hence the left/right position of the reward) were determined according to a pseudorandom schedule (Gellermann 1933). VIS.SPAT. tasks require stimulus-response and response-reward association formation but cannot be solved by direct stimulus-reward association whereas VIS.DIS. tasks can be solved by direct stimulus-reward association. This is because in VIS.SPAT. tasks both pairs of stimuli are equally associated with reward and the animal must learn a different response to each pair, whereas in VIS.DIS. tasks one stimulus is associated with reward, and is therefore chosen by the animal, while the other is not.

We have argued (Ridley et al. 1989) that "evaluative memory" (measured by stimulus-reward association tasks, e.g. VIS.DIS.) and

"non-evaluative" memory (measured by stimulus-response tasks, e.g. VIS.SPAT.) depend on separate neural substrates involving the amygdala and hippocampus respectively. Monkeys with lesions of the cholinergic projection from the nucleus basalis to the neocortex and amygdala are impaired on acquisition and retention of VIS. DIS. tasks (Ridley et al. 1986) whereas monkeys with lesions of the cholinergic projection from the diagonal band to the hippocampus and entorhinal cortex are selectively impaired on acquisition of VIS.SPAT. tasks (Ridley et al. 1988) and on various other tasks (which we have called rule-learning tasks) which they cannot solve simply by choosing the stimulus associated with reward (Ridley et al. 1989). Our prediction for the present experiment was that monkeys with fornix transection would be impaired on acquisition of VIS.SPAT. tasks but not VIS.DIS. tasks because fornix transection cuts the cholinergic projection from the diagonal band to the hippocampus.

Monkeys were initially tested on two VIS.DIS. tasks (VD1 and VD2), one VIS.DIS.BLACK (VDB1) and two VIS.SPAT. tasks (VS1 and VS2). They were then matched for learning ability and allocated to three groups. Group F (n = 10 minus 1, see histology) received fornix transections under pentobarbitone anaesthesia (20 mg/kg i.p.). Following craniotomy and unilateral meningeal incision, a small hole was made by suction in the corpus callosum at coordinates AP +7.0→+8.0 mm (Stephan et al. 1980). The bifurcation of the fornix was identified and each arm of the fornix was elevated and transected using a hooked, gauge 19, hypodermic needle under direct visual control. Group CC (N = 4 minus 1, see histology) received only a corresponding ablation in the corpus callosum, and Group U (n = 4) was unoperated.

Behavioural testing recommenced 7–14 days after surgery. All animals were tested on a new VIS.DIS. task (VD3), a new VIS. DIS.BLACK task (VDB2) and a new VIS.SPAT. task (VS3). In order to test the appropriateness of using cholinergic-rich grafts to attempt to ameliorate the learning impairment all monkeys were then tested on four further VIS.SPAT. tasks, two following injection of the cholinergic receptor agonist pilocarpine and two following injections of saline vehicle only in an alternating pattern across all tasks. Learning scores were averaged for the two tasks under saline (VS4) and pilocarpine (VS5).

Monkeys with fornix transection (Group F) were then matched on the basis of their learning impairments on VIS.SPAT. tasks VS3 and VS4 and assigned to two groups, Group FO and Group F + T. Each monkey in Group F + T (N = 5 minus 1, see histology) then received two intrahippocampal transplants on each side of a dissociated suspension of embryonic marmoset cholinergic-rich basal forebrain tissue. Twin or triplet marmoset embryos (79 days gestation, calculated as 91 days post previous parturition; 13–20 mm crown rump length) were removed from donor females by hysterotomy under general anesthesia. Cholinergic basal forebrain structures, identified in previous embryos by acetylcholinesterase histochemistry, were aseptically dissected and dissociated after brief trypsin incubation (Fine et al. 1988). Tissue from two embryonic basal forebrains, suspended in approximately 40 µl isotonic saline containing 0.6% (W/V) d-glucose and 0.01% DNase (Sigma Type I), was used for each recipient. Deposits were made at the following coordinate positions: AP 5.0 mm, Lat ± 7.0mm, Vert + 4.0 mm, + 5.5 mm; AP 1.5 mm, Lat ± 7.0 mm, Vert 7.5 mm, 9.5 mm, (Stephan et al. 1980). Thus a total of 6 deposits were made each of 1.5–2.0 µl. The non-transplanted fornix-transected animals Group FO (N = 5) underwent no further surgery. Practical constraints of using primates prevented the inclusion of a non-cholinergic tissue transplant group in this experiment but studies of transplantation to cholinergically deafferented hippocampus or cortex in rats indicate that non-cholinergic grafts have no effect on learning ability (Dunnett et al. 1982; Fine et al. 1985).

Three months after transplantation all monkeys were tested on acquisition of a new VIS.DIS. task (VD4), a new VIS.DIS.BLACK task (VDB3) and a new VIS.SPAT. task (VS6). Further attempts were then made to investigate the effect of transplantation by assessing acquisition of more difficult VIS.SPAT. tasks. Animals were tested on another VIS.SPAT. task this time using two pairs of identical BLACK objects (VSB1). They were then tested on another VIS.SPAT. task (VS7) followed 24 hrs later by the reversal of that task (VS7 Rev). In reversal learning the left/right object-reward contingency is reversed. Monkeys were next tested on a compound spatial task (SPATIAL) in which a pair of identical plaques was presented randomly over the left or the right pair of wells of a test board with four food wells. Reward was to be found first under the left hand plaque, then under the right hand plaque, then under the inner and finally under the outer member of the pair of plaques to a criterion of 9/10 consecutive correct responses for each rule. Finally, monkeys were tested on long term (6–12 weeks) retention of the VIS.SPAT.BLACK task (VSB1 Ret) followed 24 h later by reversal learning of that task (VSB1 Rev).

At the end of cognitive testing (about 9 months after fornix transection and 6 months after transplantation) all operated monkeys were perfused for histology with 10% formalin in phosphate buffered saline pH 7.4. Brain sections were cut at 40 µm thickness and stained for acetylcholinesterase (AChE) activity (Koelle 1955; Ridley et al. 1988) and/or with cresyl violet (Figs. 2 and 3).

Results

Behavioural testing

The learning scores (trials to criterion) for each task are shown in Fig. 1. For statistical analysis data were subjected to square root transformation prior to repeated measures ANOVA and task-wise post hoc comparisons using Tukey's test. Groups U and CC did not differ from each other on any task and were combined to form a single control group C. Group C and the to-be-lesioned groups FO and F + T did not differ from each other on any task prior to lesion. Groups FO and F + T did not differ on any task after fornix transection but prior to transplantation. On tasks VD3, VDB2 and VS3 (post fornix transection) there was a significant Group X Task interaction ($F(6,24) = 7.01$; $p < 0.001$). Monkeys with fornix transections (Group F i.e. Groups FO and F + T combined) were not significantly impaired in learning VD3 but were mildly impaired in learning VDB2 ($p < 0.05$) and were severely impaired ($p < 0.01$) in learning VS3, compared with Group C. On tasks VS4 and VS5 there was a significant Group X Drug interaction ($F(3,12) = 8.92$; $p < 0.005$) indicating that Group F showed a greater improvement following pilocarpine administration than Group C. Following saline injection Group F was severely impaired ($p < 0.01$) relative to Group C. This impairment was significantly reduced ($p < 0.01$) following pilocarpine injection. Pilocarpine-injected fornix-transected monkeys (Group F) were still, however, just significantly impaired relative to Group C ($p < 0.05$). Considered as two separate groups, Groups FO and F + T were both significantly impaired relative to controls following saline injection ($p < 0.01$ in each case) but they were not significantly impaired following pilocarpine injection. This result suggests that the impairment produced by fornix transection was due to disruption of the cholinergic projection rather than to transection of other hippocampal afferents and efferents.

Following transplantation there was a significant Group X Task interaction over all post operative tasks ($F(24,96) = 2.11$; $p < 0.01$). Neither Group FO nor Group F + T was impaired relative to Group C on learn-

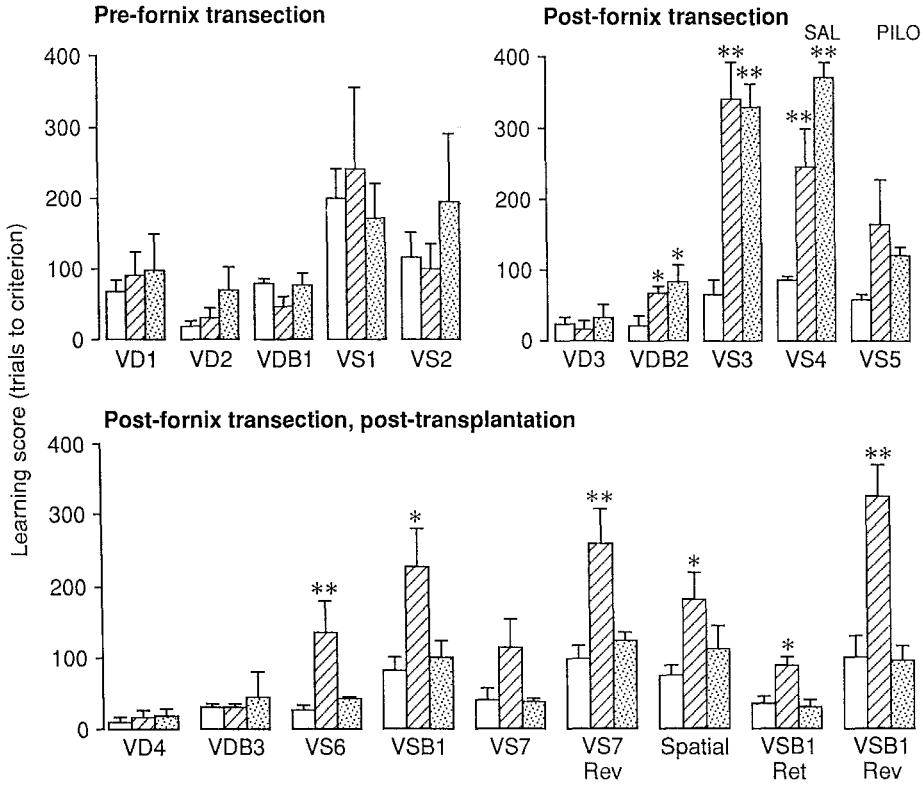

Fig. 1. This figure shows the mean learning score (trials up to criterion) for each learning task (± S.E.M.). Criterion was 27 correct responses in 30 consecutive trials (27/30) except for tasks VDl and VSl (90/100 each) and SPATIAL (4 X 9/10, see text). VD = visual discrimination; VS = visuospatial discrimination; B = black objects; Ret = retention (relearning); Rev = reversal of reward contingency. □ = Group C (corpus callosum controls plus unoperated controls, N = 7) ▨ = Group FO (fornix transected, no other surgery, N = 5) ▩ = Group F + T (fornix transected then transplanted, N = 4) SAL = 0.1 ml saline i.m. 10 minutes before daily test session PILO = Maximum tolerated dose of pilocarpine given i.m. 10 min before daily test session (usually 0.5 mg/kg; range 0.4–0.7 mg/kg). For *post hoc* comparison between Groups FO or F + T with Group C, * $p < 0.05$; ** $p < 0.01$

ing VD4 or VDB3. This indicates that the transplants did not affect the learning of tasks which were not affected by fornix transection. Group FO was severely impaired on learning tasks VS6 ($p < 0.01$), VSB1 ($p < 0.05$), VS7 Rev ($p < 0.01$), SPATIAL ($p < 0.05$), VSB1 Ret ($p < 0.05$), and VSB1 Rev ($p < 0.01$). Group F + T was not significantly impaired on any of these tasks demonstrating recovery of function in this group. As an additional measure of recovery we analysed the performance of groups across time. When performance on the last task of the experiment (VSB1 Rev) was compared with performance on the last task before any surgery (VS2), control monkeys showed no change in learning ability and monkeys in Group FO were still impaired relative to their performance prior to surgery ($p < 0.01$). The performance of the animals in groups F + T at the end of the experiment did not differ from their performance prior to surgery, i.e. they had regained their original learning ability. We then compared performance on VSB1 Rev. with performance on the first VIS.SPAT. task after fornix transection (VS3). The control animals' performance on these two tasks did not differ. The animals in Group FO also did not differ in performance on these two tasks i.e. they maintained their level of impairment throughout. The animals in Group F + T, however, showed a significant improvement ($p < 0.02$), indicating recovery of learning ability.

The monkeys with corpus callosum lesions demonstrated normal levels and patterns of AChE staining in the hippocampal formation. One animal in this group was found to have sustained a unilateral fornix transection and was deleted from data analysis. Fornix transection was confirmed by histological inspection in all Group F animals except for one animal in Group F + T where histological demonstration of fornix transection was not beyond doubt. Although initially impaired and subsequently functionally improved by pilocarpine and by transplantation, this animal was deleted from data analysis. A dorso-caudal portion of the septum had been ablated in 6 animals and showed degeneration in the remaining 3. In all FO animals loss of AChE staining was substantial throughout the hippocampal region including the dentate gyrus and entorhinal cortex but excluding the presubiculum and the most anterior part of the hippocampus which receive a projection from the basal nucleus of Meynert via a ventral route (Kitt et al. 1987). Transplants were identified bilaterally in all F + T animals as dense AChE-positive cellular masses in the temporal lobes within hippocampus, lateral ventricle, and surrounding tissue. Some fibre outgrowth distant from the transplant could be seen in all animals; in two, outgrowth into the hippocampus was substantial, yielding a pattern of AChE staining which approached that seen in normal animals (Fig. 3). Comparing performance over all post-transplant tasks, the animal with the most extensive hippocampal reinnervation learnt with fewest errors and the animal with the least extensive reinnervation committed the most errors. Nevertheless it must be emphasized that all transplanted animals showed complete recovery relative both to the control animals and to their own pre-lesion performance, and their overall learning scores were very similar to each other. No adverse effects

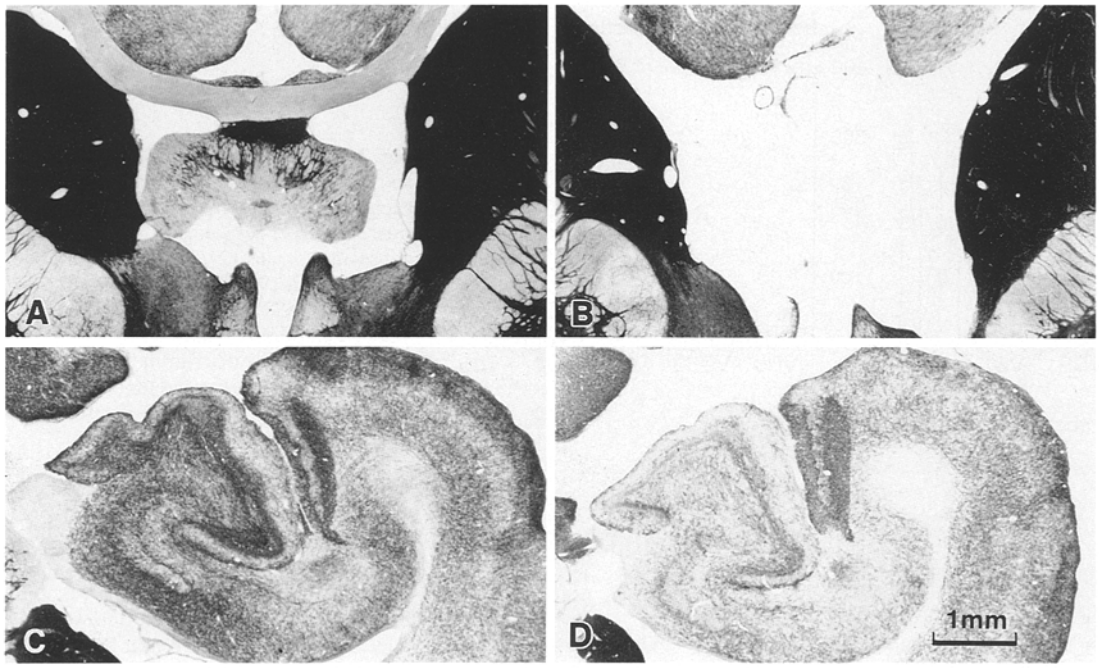

Fig. 2A–D. Photomicrographs of **A** intact fornix; **B** transected fornix; **C** hippocampus of monkey shown in **A**; **D** hippocampus of monkey shown in **B**. 40 μm sections stained for AChE and lightly counterstained with cresyl violet to reveal granule cells of the dentate gyrus. Note severe loss of AChE staining in hippocampus including dentate gyrus but not in presubiculum in the lesioned monkey

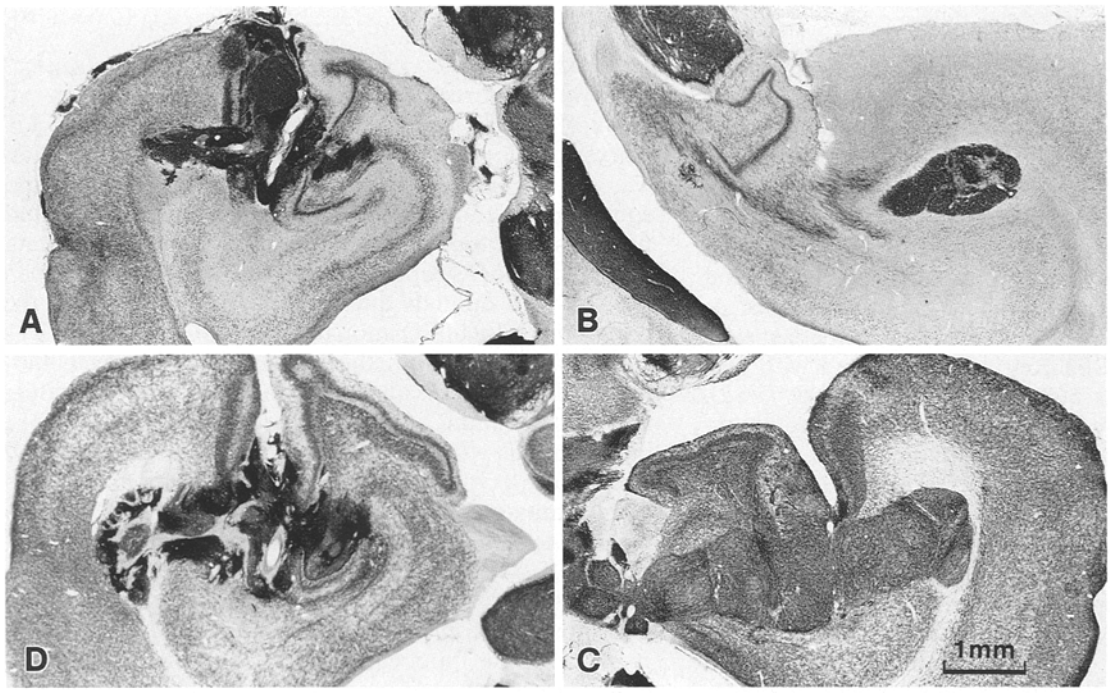

Fig. 3A–D. AChE-stained sections illustrating transplanted tissue in each monkey in Group F+T. Transplants **A**, **B** showed patchy fibre outgrowth, and **C**, **D** showed substantial outgrowth with restoration of normal laminar patterns of hippocampal cholinergic innervation

of transplantation were observed in any F+T animal in task performance, general behaviour or health. Although donors and recipients were in all cases unrelated and no immunosuppressives were used, there was no histological evidence of graft rejection in any transplanted animal.

Discussion

These results demonstrate that transplants of embryonic cholinergic-rich neural tissue completely restored learning ability in fornix-lesioned monkeys across a range of

task difficulties on visuospatial tasks. Since impairment on these tasks is demonstrated by the commission of errors of choice, the impairment cannot result from dysfunction of motivation or motor ability. Furthermore, since the same sorts of objects are used in both visuospatial and visual discrimination tasks on which fornix-lesioned monkeys are not impaired, the impairment cannot involve dysfunctions of attention or perceptual analysis. Rather, the impairment and its amelioration by transplants seem to involve alterations in a specific learning ability. This impairment is specific to the formation of associations between object stimuli and spatial responses although previous work involving lesion of the diagonal band, which also deprives the hippocampus of its cholinergic input, produces impairment on acquisition of visuospatial tasks and on other conditional tasks which require the formation of associations between object-stimuli and other objects or the choice between objects matched for secondary reinforcing properties (Ridley et al. 1989). It therefore seems likely that the visuospatial tasks on which fornix-lesioned animals are impaired is one example of a broader category of tasks for which hippocampal function is essential for successful performance. We have termed this sort of memory non-evaluative memory or rule-based learning (Ridley et al. 1989) in contrast to evaluative memory (the acquisition of secondary reinforcing properties) which is dependent on the function of the amygdala.

Results showing that pilocarpine can at least partially restore learning ability in fornix transected monkeys suggests that the impairment is due mainly to interruption of the cholinergic projection from the vertical limb of the diagonal band and septum to the hippocampus and that the transplant-induced recovery may be due to release of acetylcholine from grafted tissue. We have previously shown significant but incomplete restitution of cognitive function by pilocarpine in monkeys with lesions of the diagonal band (Ridley et al. 1988) and complete restitution of function by pilocarpine in monkeys pretreated with hemicholinium (Ridley et al. 1987).

Cholinergic grafts to hippocampus or cortex, presumably lacking normal presynaptic inputs and thus normal patterns of activity, can restore cognitive function in rodents (Dunnett et al. 1982; Fine et al. 1985). Thus acetylcholine may have a facilitatory role in hippocampal and cortical activation which is not dependent on precisely patterned activity in the cholinergic input. Electrophysiological data (Krnjevic and Ropert 1982; Nicoll 1985) indicate that acetylcholine acts upon hippocampal neurones in such a manner as to increase the effectiveness of other inputs in stimulating action potentials. Previous experiments in rodents have shown that cholinergic-rich neural tissue transplants can correct EEG abnormalities caused by fornix transection or basal nucleus lesions (Buzsaki et al. 1987; Vanderwolf et al. 1990). Cholinergic transmission can facilitate hippocampal long term potentiation (Ito et al. 1988), a phenomenon which may underlie the involvement of the hippocampus in certain specific learning abilities (Morris et al. 1986). Thus the neural tissue transplants in the present experiment may restore learning ability by releasing acetylcholine in the hippocampus.

Since it is known that cholinergic transplants form patterns of innervation at both the light and ultrastructural level which are similar (but not identical) to normal (Clarke et al. 1986) and that acetylcholine release from intrahippocampal septal grafts can be physiologically modulated by the host (Nilsson et al. 1990), such transplants may be able to provide a more physiologically appropriate level of cholinergic input into the hippocampus than can be produced by injection of cholinergic agonists. This may account for the ability of the transplant to produce greater restoration of function than the agonist treatment.

Grafts of embryonic dopamine-rich tissue have led to partial restoration of motor function impaired by prior neurotoxin-induced dopamine depletion in rodents (Freed et al. 1980; Björklund et al. 1980) and primates (Redmond et al. 1986; Fine et al. 1988; Annett et al. 1989) and similar procedures are currently being assessed in humans as an experimental treatment for the motor disorder of Parkinson's disease (Hitchcock et al. 1988; Madrazo et al. 1988; Lindvall et al. 1989, 1990). The cerebral cholinergic system is known to be damaged in Alzheimer's disease, Parkinson's disease with dementia and Korsakoff's syndrome and the degree of disability is correlated with post-mortem measures of cholinergic dysfunction (Bowen et al. 1976; Perry et al. 1985; Arendt et al. 1983). Although extensive further experimentation in primates with experimentally induced conditions more closely resembling the human disease states is called for, the results presented here suggest that cholinergic transplantation may have a role in treating the cognitive dysfunction of these disorders.

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