REVIEW ARTICLE

Mechanisms of Action of Neural Grafts in the Limbic System

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ABSTRACT: This review summarizes the range of possible mechanisms of action of neuronal grafts in the central nervous system. It aims to illustrate the capacity and limitations of the transplanted tissue in the promotion of neurological recovery after experimental surgical insults.

RÉSUMÉ: Des mécanismes d'action et les effets d'une greffe sur le système nerveux. Cette étude présente un sommaire de toute une gamme de méchanismes d'action possible et les effets d'une greffe sur le système nerveux. Le but de cette étude est de faire valoir la capacité et limitation du tissu transplanté après un trauma expérimental chirurgical pendant la récupération neurologique.

Can. J. Neurol. Sci. 1988; 15:99-105

The septohippocampal system, which is the focus of this review, offers several distinct advantages for studies of the action and effects of neural grafts in the central nervous system: (1) the hippocampus possesses electrical rhythms which vary with ongoing behavior in a specific manner, (2) the excitability changes within the hippocampus are easy to monitor, (3) the subcortical and neocortical inputs-outputs to and from the hippocampus are anatomically segregated and can therefore be selectively damaged, (4) the afferents terminate in a characteristic laminar fashion, and (5) the physiological effects of several afferent paths are relatively well understood.

Lesion and Grafting Procedures

Surgical elimination of the subcortical afferents to the hippocampus is achieved by aspirating the fimbria, the dorsal fornix, the ventral hippocampal commissure, part of the corpus callosum, the cingulum bundle, the supracallosal striae and part of the cingulate cortex. The lesion eliminates the afferent brainstem projections from the locus coeruleus and the raphe nuclei, as well as all of the septohippocampal afferents to the anterior two-thirds of the hippocampus. In addition, the subcortical output from the hippocampal formation, comprising a feedback loop to the septal area and the extrapyramidal system, is severed. The aspiration cavity extends through the septal pole of the hippocampus exposing the vessel-rich surface overlying the anterior thalamus, which serves as a receptacle for solid grafts.[1] Suspension of fetal brain cells are injected directly into the deafferented host hippocampus.[2] In most experiments the surgical lesion and transplantation are made unilaterally, thus allowing comparison with the intact hemisphere.

Electrical Activity of the Normal and Deafferented Hippocampus

The most characteristic hippocampal EEG pattern is the rhythmical slow activity (RSA or theta rhythm), which in the rat occurs during exploratory behaviors (walking, running, rearing, sniffing) and the paradoxical phase of sleep.[3] The sources of rhythmicity are the cholinergic and GABAergic "pacemaker" cells of the medial septum and the nucleus of the diagonal band of Broca.[4] In the freely moving rat two types of theta patterns coexist. One type is cholinergic-muscarinergic and can be eliminated by scopolamine or atropine. The other type of theta is resistant to cholinolytics.[5]

Another pattern of spontaneous hippocampal activity is the irregularly occurring sharp waves (SPW) of 40-120 ms duration. SPWs are observed during immobility and consummatory behaviors (drinking, eating, face washing, body grooming) and never occur during behaviors accompanied by RSA.[6,7,8] SPWs are invariably correlated with the synchronous discharge of a number of pyramidal cells, granule cells and interneurons. It is hypothesized that SPWs are triggered by a population burst of CA3 pyramidal cells as a result of temporary disinhibition from afferent control.[6]

Subcortical deafferentation of the hippocampus results in marked and permanent changes of the hippocampal electrical patterns. RSA is absent completely and is replaced by low amplitude fast activity during exploratory behavior. The incidence and amplitude of SPWs may be increased and can also occur during behaviors normally associated with RSA, although at a lower probability than during immobility and consummatory behaviors. In animals with fimbria-fornix lesions SPWs in the

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This review is based on a paper presented by Dr. Gage as part of a symposium on Regeneration and Restorative Neurology at the 1987 Canadian Congress of Neurological Sciences

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two hippocampi occur asynchronously. In addition to the SPWs, short duration (<50 msec) and very large amplitude (up to 6 mV) EEG spikes can occur, although at a lower probability. Occasionally, population spikes are seen riding on these interictal transients. In the deafferented hippocampus the threshold of seizures, induced by low frequency (5 Hz) stimulation of the perforant path, is significantly lower than in the intact hippocampus.[9] This pathological activity of the deafferented hippocampus may worsen the function of its targets via its remaining efferents. In addition, our preliminary experiments indicate that high frequency stimulation of the perforant path fails to induce long-term potentiation in the denervated hippocampus.[10]

Restoration of Theta Activity by Graft Bridges

In an attempt to reveal the physiological mechanisms for the behavioral improvements observed in bilaterally lesioned and grafted animals,[11-14] we investigated the activity of the deafferented host hippocampus after transplanting fetal tissue into the lesion cavity or directly into the host hippocampus. The most striking reparative change we observed was the reappearance of hippocampal RSA with septal and hippocampal bridges (Figure 1). Concurrent with RSA, granule cells and interneurons fired rhythmically, phase-locked to RSA. Cross-correlation of EEG from the transplanted and intact sides revealed that RSA in both hippocampi was in-phase, suggesting that both hippocampi were modulated by the same "pacemaker" group of neurons. Similar to normal rats, RSA was present only during running and walking and absent during behavioral immobility and drinking. The depth profile and the septo-temporal distribution of the power of RSA correlated with the density and distribution of the graft-mediated acetylcholinesterase (AChE)-positive reinnervation of the host hippocampus.[15] Considerably better restoration was found with solid septal than with solid hippocampal graft bridges.

Suspension grafts did not restore behavior-dependent RSA in the host hippocampus. Rhythmic EEG waves and phase-locked unit firing for up to several seconds were occasionally observed in the rats of the septal suspension group, but only during immobility. These rhythmic-waves may have been produced by the transplanted septal cells or by abnormal afferents from the thalamic spindle-pacemaker neurons.

Possible Mechanisms of Graft-mediated Recovery of RSA

The findings that RSA recorded from the intact and reinnervated hippocampi was highly coherent, and temporally related, and that septal cells injected directly into the host hippocampus did not produce behavior-dependent RSA led us to hypothesize that axons of the host septal neurons grew back across the fetal tissue bridge and contacted their normal target cells. According to this passive bridge model the graft tissue merely served as a scaffold to induce and guide regeneration of the severed septohippocampal connections.

Following fimbria-fornix transection 60 to 80% of the cells in the medial septum and diagonal band of Broca undergo degeneration.[16] Consequently, we assume that the few remaining septal cholinergic cells were sufficient for maintaining a pacemaker rhythmicity, and through their regrown axon terminals they were able to modulate the synaptic membranes of a sufficient number of hippocampal neurons to result in rhythmic extracellular current flow. Another explanation for the highly correlated RSA in both hippocampi would be that the denervated hippocampus was reinnervated by axon collaterals of the contralateral septal area cells. Under normal conditions the crossed septohippocampal projection is minimal,[17] but vacant synaptic sites and trophic factors released as a result of the surgical lesion[18,19] might induce sprouting, resulting in stronger-than-normal crossed projections. This possibility is supported by our anatomical tracer experiments. In rats with unilateral fimbria-fornix transection and hippocampal implants into the lesion cavity we injected the fluorescent dye fluorogold into the denervated hippocampus. In these experiments labeled neurons were found not only in the ipsilateral septum but also in the contralateral side. The ratio of the labeled cells in the contra- and ipsilateral septum was higher than what might be expected on the basis of normal anatomical distribution.[17]

Combination of Fetal Grafts and Nerve Growth Factor (NGF) Treatment

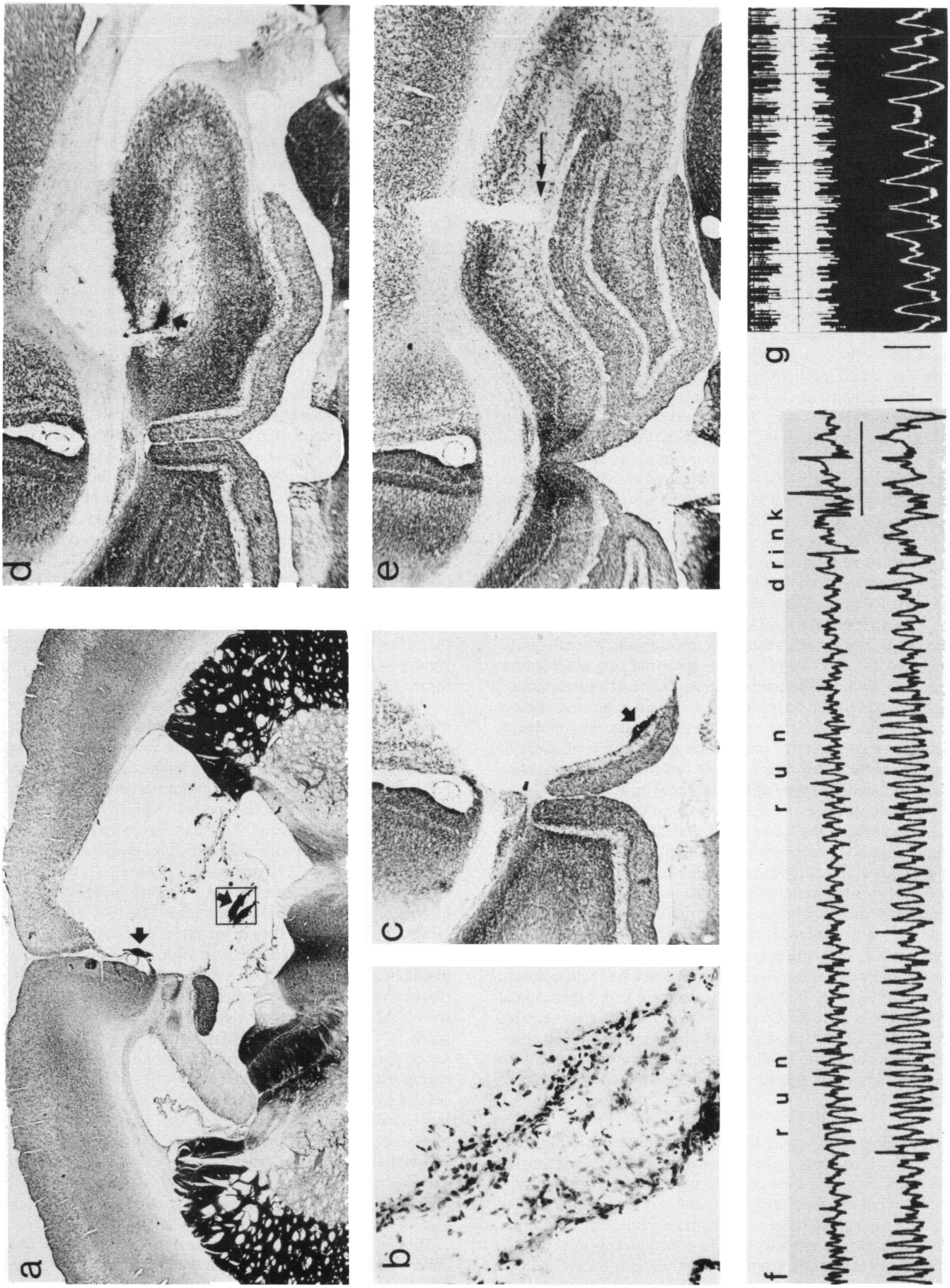
It has been speculated that neuronal death in the septal area following experimental damage of the fimbria-fornix and in Alzheimer's disease may be due to either the loss, inappropriate delivery, or dysfunctional utilization of neurotrophic factors. Such neurotrophic factors may be derived from target neurons and/or supporting glial cells.[19,20,21] Several neurotrophic factors have been detected in the hippocampus and retrogradely transported specifically to neurons of the basal forebrain.[19,21] Moreover, exogenous NGF has been shown *in vivo* and *in vitro* to stimulate choline acetyltransferase (ChAT) activity of these cells in both developing and adult animals.

In addition, it has been reported recently that intermittent or continuous infusion of NGF through an intraventricular cannula device promoted the survival of neurons in the medial septum and the nucleus of the diagonal band after partial[20] or complete[22,23] transection of the fimbria-fornix.

Following complete damage to the fimbria-fornix, NGF treatment resulted in the survival of 80-100% of both cholinergic and non-cholinergic neurons in the vertical limb of the diagonal band. In the medial septum NGF infusion lead to a sparing of 60-80% of the cholinergic neurons and 50% of the total neurons (Nissl-sections) relative to the brains with surgical lesions only.[23] These findings thus demonstrate that intraventricular infusion of NGF leads to a substantial protection of neurons of the septal region following axotomy, and support the hypothesis that death of the transected neurons is due to the loss of target-derived endogenous neurotrophic factors. This suggestion is further supported by experiments showing that after termination of NGF treatment, neuronal death occurs.[22]

Fetal hippocampus placed into the fimbria-fornix cavity did not promote survival of the neurons in either the medial septum

*Figure 1 — Graft-induced return of RSA in the denervated hippocampus. Survival: 8 months, **a,c,d,e:** AChE-stained sections at the level of fimbria-fornix lesion and the recording track (double arrow in **e**). Arrows indicate densely stained septal graft segments. The part in the boxed area is in **a** is shown at a higher magnification in **b**. Nissl staining reveals neuronal perikarya in the graft. **f:** EEG activity derived from the right (above) and the left (intact, below) hippocampi during running and drinking. Note the similarity between EEG pattern from both hippocampi. **g:** granule cell activity and simultaneously recorded EEG from the reinnervated (right) hippocampus during running. Note rhythmical firing of cells and the relationship between unit activity and EEG. Calibrations: **f:** 1 s, 1 mV; 0.5 s (scale bar is in **f**), 0.5 mV (EEG), 0.1 mV (unit). Reprinted with permission from **Brain Res.** 400(1987) 334-347.*



https://doi.org/10.1017/S0317167100027438 Published online by Cambridge University Press

or the diagonal band. The percentage of cell loss in the transplanted rats was essentially similar to that in rats with fimbria-fornix lesion only.[24] The failure of fetal hippocampal implants to protect the septal area cell loss may be accounted for by a recent finding that the NGF and NGF messenger-RNA content of the hippocampus is very low at birth and begins to increase significantly only during the second postnatal week.[25] The low NGF level in the transplanted hippocampus during the first one or two weeks after transplantation may explain its inability to protect the neurons from dying in the septal area. We tested this hypothesis by combining a hippocampal graft, placed into the fimbria-fornix cavity, with a transient (2 weeks) NGF-infusion into the lateral ventricle. After seven months of survival, the rats were tested electrophysiologically, and following histological processing, the ChAT-positive cells in the medial septum were counted. The combined treatment resulted in a permanent saving of 30% of the septal cholinergic cells which otherwise would have died. AChE-positive reinnervation of the host hippocampus was heavier than in the transplant only group, and occasionally hyperreinnervation of the dentate gyrus was observed. Interestingly, the septotemporal extent of the AChE-reinnervation was similar to the graft only group. In accordance with the anatomical recovery, restoration of theta activity and phase-locked firing of neurons was observed in the reinnervated parts of the host hippocampus.[15]

In all of the experiments above, restoration of normal or near-normal electrophysiological patterns was observed only in the anterior part of the hippocampal formation. The remaining part displayed electrical patterns similar to those observed in rats with lesion only. Also, peripheral administration of the cholinergic blocker scopolamine completely abolished the graft-mediated theta activity.[24] In the behaving rat, scopolamine cannot eliminate all theta activity from the intact hippocampus.[5] Further experiments are needed to attain a more complete reinnervation of the host hippocampus via the fetal bridge in order to see recovery of physiological function in all areas of the hippocampus and to investigate the possibility of restoring the non-cholinergic type of hippocampal theta activity.

In a separate series of experiments we investigated the ability of grafted cells to modulate the excitability of the deafferented hippocampus. In rats with bilateral fimbria-fornix lesions and suspension grafts of locus coeruleus neurons, the incidence of interictal spikes was much lower than in the lesion only group. In addition, locus coeruleus grafts virtually eliminated the picrotoxin (1 mg/kg) induced behavioral seizures. In contrast, in animals with suspension grafts of hippocampal cells, the frequency of interictal transients was several times higher than in the control group. In 50% of the animals with hippocampal grafts, spontaneous EEG and/or behavioral grand mal seizures were observed.[26-28] These findings are in agreement with independent observations that locus coeruleus grafts may delay the onset of behavioral seizures in a kindling model of epilepsy.[29]

Host-graft Interactions

Recordings from solid hippocampal grafts revealed the presence of both complex-spike units (pyramidal cells) and single-spike units (granule cells and interneurons). A portion of the neurons changed their firing rates and discharge patterns as a function of ongoing behavior. About one-eighth of the single-spike cells fired rhythmically and phase-locked to the RSA recorded concurrently from the contralateral (intact) hippocampus.[30,31] These findings indicate that at least some neurons in the hippocampal graft are reinnervated from the host septum and their activity is regulated in a physiologically relevant manner.

Graft neurons could be activated by stimulating the ipsilateral hippocampus or the ipsilateral perforant path, with latencies of 8-30 msec. The functional relevance of the host-graft connections is demonstrated by the long-term potentiation (LTP)[32] of the evoked graft activity following high frequency stimulation.[27] This experiment is particularly interesting in light of our finding that LTP is missing in the subcortically deafferented hippocampus. Together these experiments suggest that the transplanted hippocampus is innervated by subcortical afferents whose presence is essential for plastic changes in the hippocampus.

The most typical EEG pattern of the graft was an EEG spike with a duration of 20 to 200 msec. The amplitude of the EEG spikes varied between 0.2 and 5 mV, and their frequency varied between 0.1 to 10 Hz. Sometimes the EEG spikes occurred in bursts of 2 to 10 waves. EEG spikes were correlated with synchronous discharges of several neighboring units. Single-spike units (putative interneurons) could fire up to 100 action potentials at 500-700 Hz during an EEG spike-associated burst, indicating that they were strongly excited by the principal cells. As discussed above, SPWs are also present in the normal hippocampus during immobility and consummatory behaviors. However, EEG spikes in the graft were also present during behaviors normally associated with hippocampal RSA. Simultaneous recording from the host hippocampus close to the graft revealed that the EEG spikes frequently invaded the host hippocampus. Occasionally, spontaneous seizures initiated in the graft were observed to propagate to the host hippocampus.[30] Neuronal connections between the graft and host were confirmed by anatomical tracer studies.[27]

The high level of excitability of the graft neurons is reflected in our observations that complex spike neurons frequently discharged 5 to 8 action potentials spontaneously or in response to electrical stimulation of the host hippocampus or perforant path, while complex-spike cells in normal rats never respond with more than one spike to stimulus volleys.[33,34]

The increased synchrony of cell discharges may be explained by assuming that neurons in the graft receive axon terminals mainly from intrinsic cell populations. Consequently, the incidence of collateral excitation may be higher than in the normal hippocampus. Also, GABAergic inhibition may be less efficient in the transplant than in the intact hippocampus.

Our electron microscopic observations lend support for both possibilities. Although GABAergic cells were present in the hippocampal graft,[35] the number of chandelier or axo-axonic cells[36,37] were reduced or missing completely in the hippocampal grafts.[27,38] Since the axon initial segment is a crucial site for action potential generation, lack of inhibitory influence in this region may result in increased firing of the cell. In addition, several asymmetric, non-GABAergic synapses were found on the somata of pyramidal cells in the graft. In the normal hippocampus only symmetric synaptic contacts surround the cell bodies of pyramidal neurons. Asymmetric, presumably excitatory, synapses on the soma may provide an especially effective synaptic drive because their effects are less attenuated by distal inhibitory influences.

The transplanted hippocampus thus may be regarded as an epileptic focus, and could explain the high incidence of behav-

ioral seizures in animals with cell suspension grafts of the fetal hippocampus.

Behavioral Studies of Graft Action

Bilateral fimbria-fornix lesions in rats are known to result in severe impairments in learning and memory.[39,40] In addition, these same types of impairments can be obtained by pharmacological blockade of cholinergic transmission in a variety of tests.[41,42] Using several standard behavioral tests of learning and memory, researchers have demonstrated the ability of the fetal septal grafts to reverse these impairments. In the eight arm radial maze rats with septal grafts (7 months after transplantation) showed a positive linear trend in maze performance over days of testing, but did not differ significantly from nongrafted rats with lesions overall.[13] However, potentiation of the cholinergic transmission by pretreatment with physostigmine produced a significant enhancement of maze performance in the grafted group, but not in the lesioned control group, and in some cases the grafted rats performed as well as the nonlesioned control animals.

In another study,[11] using a T-maze forced choice alternation test performed 6 months after transplantation, seven out of nine rats with solid septal grafts and four out of five rats with septal cell suspensions learned the task, some of them up to the level of the control rats. The remaining rats with septal grafts, and a separate group of rats with locus coeruleus grafts, performed at chance level, similar to the rats that only received the fimbria-fornix lesion. In this study there was a positive and significant correlation between performance of the grafted rats and the amount of graft derived AChE positive staining in the previously denervated hippocampus.

In a more recent study[14] septal cell suspension grafts, implanted into the hippocampal formation in rats with bilateral fimbria-fornix lesions, were found to improve spatial learning also in the Morris[43] water maze task. This was seen both in rats which had been pretrained in the task prior to lesion and grafting, and in rats which had not been exposed to the water maze prior to lesion and transplantation. In the pretrained rats, the bilateral fimbria-fornix lesion completely abolished the acquired performance, and while the lesioned rats could accomplish the task partially using nonspatial strategies, most of the septal grafted rats were able to reacquire a spatial memory of the platform site. Interestingly, atropine (50 mg/kg) completely abolished the reacquired spatial memory in the grafted animals. This atropine effect was seen also in the normal control rats, but to a lesser extent.

Together these studies strongly suggest not only that the grafts can partially ameliorate deficits in spatial learning that result from fimbria-fornix lesions, but that the amelioration shows some specificity for the septal grafts which provide a cholinergic reinnervation of the deafferented hippocampal formation.

Possible Mechanisms of Behavioral Improvement by Grafts in the Denervated Hippocampus

The major input to the hippocampus arrives from the entorhinal cortex. In the absence of the subcortical direct or feed-forward inhibition the afferent neuronal template from the entorhinal input is amplified by the SPW-associated mechanisms and the unprocessed signal pattern is fed back to the entorhinal cortex via the subiculum.[6,7] The returned and magnified afferent template may interfere with the activity of the entorhinal cortex as well. This mechanism may explain why sectioning of the fimbria-fornix is more devastating to behavior than selective removal of 90% of the neurons from the hippocampus by ibotenic acid lesion.[44] The amplifying, reverberating role of the hippocampus appears essential for the development of kindling, epilepsy and ischemia-induced cell death. Interference with the amplifier chain of the neocortico-hippocampal circuitry by surgical lesion of the perforant path or ibotenic-acid lesion of the granule cells retards kindling, abolishes behavioral seizures, and protects neurons from death.[45,46,47] Under normal circumstances the subcortical inputs provide stability to the entorhino-hippocampal system.[6,9,48]

Viewed from this perspective, grafts restoring the subcortical control of the hippocampus appear ideal for behavioral recovery. Thus, the nearly perfect reappearance of the electrical activity of the host hippocampus in some animals with solid grafts could be taken to indicate that the "bridging" technique may be more efficient than suspension grafts in attempts to restore behavioral deficits. Indeed, behavioral deficits in different types of spatial tasks in fimbria-fornix damaged rats were significantly improved by solid septal grafts placed into the lesion cavity although subcortical afferents were not restored in these animals, and the electrophysiological consequences of septal graft bridges and suspension injections, as shown above, are very different.

It should be emphasized, however, that reinnervation and restoration of theta from graft bridges were restricted to the septal pole of the host hippocampus. Thus, even if normal function reappeared completely in the anterior part of the host hippocampus, the physiological activity of the major portion of the structure remained similar to fimbria-fornix lesioned animals.

In rats with suspension grafts of septal tissue at two or three levels along the septotemporal axis of the hippocampus, subcortical control is not reestablished, but reinnervation of the host hippocampus by AChE-positive fibers is nearly complete.[2,13,14,49] It is possible that the non-regulated cholinergic and/or GABAergic cells of the graft suppressed the deleterious amplifying action of the host hippocampus.

Furthermore, it is possible that the axons of the host hippocampus contact the grafted septal cells, thereby establishing a regulatory feedback circuitry between the host and graft. Direct recording from the transplanted septal cells may determine the regulated or nonregulated nature of the suspension graft cells.

An additional cause of the behavioral deficit seen in fimbria-fornix animals may be due to the lack of synaptic plasticity in the deafferented hippocampus. Long-term potentiation is thought to represent a laboratory model for memory trace formation.[50-52] Suspension grafts placed directly into the hippocampus may restore the impaired synaptic plasticity and may facilitate behavioral recovery.[53]

Our electrophysiological analyses, as summarized above, suggest that behavioral improvement may be obtained by merely suppressing the pathological electrical patterns of the denervated hippocampus which may interfere with the normal activity of its target structures. This mechanism of behavioral improvement would thus not necessarily reflect real restoration, but rather suppression of abnormal activity. The graft may work as a regulated short circuit which may abridge noise-producing modules in the brain machinery. It remains an excit-

ing challenge for future transplantation experiments to produce more extensive behavioral recovery by real restoration of physiological function.

Acknowledgements

This work was supported by the J.D. French Foundation, the National Institutes of Health (NS-6705, AAG-06088), the California State Grant (86-89619), and the Margaret and Herbert Hoover Foundation. We thank Sheryl Christenson for typing the manuscript.

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https://doi.org/10.1017/S0317167100027438 Published online by Cambridge University Press