

FUNCTIONAL EFFECTS OF LESION-INDUCED PLASTICITY: LONG TERM POTENTIATION IN NORMAL AND LESION-INDUCED TEMPORODENTATE CONNECTIONS

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SUMMARY

The crossed temporodentate pathway from the entorhinal cortex of one hemisphere which proliferates in response to a contralateral entorhinal lesion in adult rats was analyzed for its ability to exhibit long term potentiation of synaptic efficacy similar to that which occurs in the normal ipsilateral temporodentate pathway. It was found that while the small synaptic response evoked by contralateral entorhinal cortical stimulation in normal rats does not undergo long term potentiation, after unilateral entorhinal lesions and proliferation of the crossed temporodentate pathway, the crossed pathway acquires a capacity for potentiation of synaptic action which qualitatively resembles that of the normal ipsilateral temporodentate circuit. However, despite the potentiation of synaptic drive, no long term enhancement of cell discharge was observed in the re-innervated dentate gyrus even though potentiation of this parameter was very prominent in the ipsilateral pathway. Mechanisms are discussed by which a previously non-potentiating pathway may acquire, as a consequence of lesion-induced sprouting, an ability to undergo long term potentiation of synaptic efficacy in a fashion similar to the ablated pathway. Reasons for the failure to observe potentiation of cell firing are also considered.

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INTRODUCTION

Neuroanatomical studies on diverse systems in the brains of both developing and mature mammals have established that partial deafferentation of a neuronal population is often followed by growth and reorganization of surviving afferent projections to the denervated cells (sprouting)^{8,11,17,20,21,22,33}. Interpretation of the functional significance of such sprouting has been confounded by issues of specificity in the relationship between ablated and sprouting afferent systems. For example, it is difficult to envision how sprouting of afferents anatomically and functionally dissimilar to those destroyed by a lesion could restore normal input patterns to and activity in denervated target neurons. Such a process would seemingly create aberrant neural circuitry which, if functional, might further complicate lesion related deficits^{18,21}. However, in systems where deafferentation is followed by synaptic replacement via pathways which are anatomically and electrophysiologically related to the ablated connections, conditions may be optimized for sprouting to contribute to functional recovery by restoring relatively normal patterns of afferent activity.

One system which exhibits lesion-induced sprouting of an homologous afferent has been found in the dentate gyrus of the rat hippocampal formation. Unilateral entorhinal cortical ablation destroys the normally massive perforant path input to the ipsilateral dentate gyrus (ipsilateral temporodentate pathway) and induces reactive changes in a number of surviving afferent systems^{16,17,19,24,36,37}. In particular, a normally small crossed projection from the contralateral entorhinal region⁷ proliferates extensively to reinnervate a portion of the denervated zone in the rostral dentate gyrus^{24,25,27,38}. Because this lesion-induced crossed temporodentate pathway exhibits a topographic organization similar to that of the normal ipsilateral temporodentate projection^{26,38} and because this crossed pathway is formed by collaterals of entorhinal cells which also contribute an axonal branch to the ipsilateral pathway²⁸, these two pathways are considered anatomically homologous.

This anatomical homology between the normal ipsilateral and lesion-induced crossed temporodentate pathways has led us to undertake a detailed electrophysiological comparison of the synaptic properties of the two projections in order to ascertain the extent to which sprouting of the contralateral input can restore functional properties characteristic of the ipsilateral pathway. The normal ipsilateral temporodentate circuit has been well characterized electrophysiologically as a powerful monosynaptic excitatory input¹⁴. It is further distinguished by a remarkable capacity for synaptic plasticity such that specific stimulation patterns may produce such modifications in transmission as habituation^{9,32}, frequency facilitation¹³, paired pulse potentiation^{15,29,30}, or long term potentiation (LTP)^{2,3,5}. To date, the lesion-induced crossed pathway has been demonstrated to be monosynaptic and excitatory^{25,27} and to possess a capability for habituation⁹ and paired pulse potentiation²⁹, which closely resembles that of the ipsilateral pathway. The present investigation extends this comparison of synaptic properties by demonstrating synaptic LTP in the lesion-induced crossed temporodentate circuit. In contrast, an additional series of experiments on the relatively small normal crossed temporodentate pathway does not show LTP, suggest-

ing that some alteration in the synaptic properties of this projection may occur as a consequence of sprouting.

METHODS

Two groups of adult, male Sprague–Dawley rats served as subjects in this study. In one group, sprouting of the crossed temporodentate pathway was induced by placing electrolytic lesions unilaterally in the entorhinal cortex in accordance with previously described ablation procedures¹². These animals then survived for at least 30 days prior to their use in acute electrophysiological experiments. The second group of rats was unoperated at the time they were used in acute experiments.

For electrophysiology, animals were anesthetized with chloraloseurethane ($55\frac{1}{N}$ mg/kg and 0.2–0.4 g/kg respectively), and the neocortex overlying hippocampal and entorhinal cortical regions was surgically exposed. A bipolar twisted wire stimulating electrode was stereotaxically positioned above the entorhinal cortex (1.5 mm anterior to the transverse sinus, 3–4 mm lateral to midline, 10° angle from midline) or, in some experiments, above the angular bundle through which entorhinal efferents pass as they project out of the entorhinal region (2.5 mm anterior to the sinus, 4 mm lateral to midline). Micropipette extracellular recording electrodes filled with 4 M NaCl (5–15 M Ω tip impedance) were positioned over the ipsilateral and/or contralateral dentate gyrus (3.5 mm posterior to bregma, 1.5 mm lateral to midline). All electrodes were then lowered into the brain and their positions adjusted as necessary to produce optimal evoked responses in the dentate gyrus.

In most experiments on unoperated rats, two ipsilateral recording electrodes were used to permit simultaneous direct recording of the dentate synaptic layer population EPSP and the cell body layer population spike. In other normal animals both ipsilateral and contralateral dentate synaptic responses to entorhinal stimulation were recorded. Similar paradigms were followed in experiments on operated animals. Either ipsilateral and contralateral dentate responses were recorded simultaneously or two recording electrodes were placed in the dentate gyrus contralateral to the site of stimulation to simultaneously record the extracellular EPSP and population spike.

Extracellular evoked potentials were amplified and printed on line after signal averaging using a Nicolet Model 1072 Instrument Computer. FM recordings of responses were also made for further analysis. Stimuli were monophasic, constant voltage pulses of 0.3 msec duration generated by an Ortec Model 4710 Dual Channel Stimulator and delivered using WPI Stimulus Isolation Units. At the end of the experiments, animals were sacrificed using an overdose of urethane or Nembutal and perfused with a 10% formalin/0.9% saline solution. The brains were removed, sectioned, and processed histologically for cresyl violet staining to facilitate identification of electrode tracks and the extent of entorhinal lesions. The efficacy of lesions in destroying entorhinal efferents was determined in sections stained for acetylcholinesterase¹⁶.

Experimental procedure

Experimental procedures in normal and operated animals were similar. After

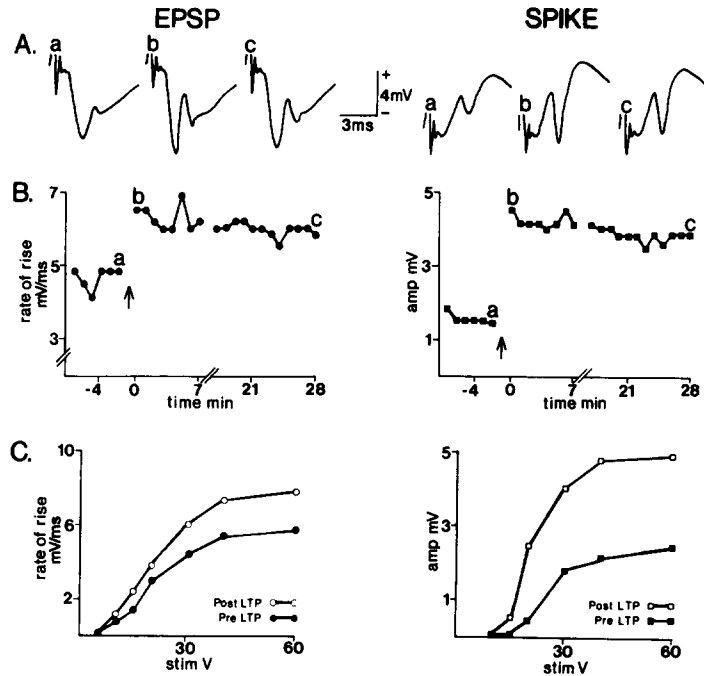


Fig. 1. Long term potentiation (LTP) in the normal ipsilateral temporodentate circuit. The population EPSP (left column) and population spike (right column) were simultaneously recorded. Each response and data point represents a computer average of 4 evoked potentials. A: sample averaged evoked potentials obtained immediately prior to (a), immediately following (b) and 28 min following (c) 400 Hz conditioning. The responses correspond to points a, b, and c respectively in B. B: LTP of test responses. The test stimulus was delivered at 30 V at a rate of 0.05 Hz. LTP was induced by replacing 8 test pulses with 60 V, 20 msec, 400 Hz trains (↑). The break between post-LTP points b and c represents an 8 min period during which the post-LTP input-output function of C was recorded. C: pre-LTP and post-LTP stimulus intensity-response magnitude relationships (input-output functions)

electrode positions had been optimized to record the maximal population EPSP or population spike, the prepotentiation stimulus-response relationship was determined by raising the stimulus intensity in increments from threshold to that producing the maximum response. A test stimulus was selected at an intensity midway along this range and delivered at low frequency (0.1–0.05 Hz) to establish a test response baseline. LTP of the responses was then induced either by delivering a long (15–20 sec) pulse train at relatively low frequency (15–50 Hz)², or by delivering 6–8 20 msec trains of 400 Hz pulses⁴. Single test pulses were then resumed and postconditioning input-output functions were obtained at predetermined intervals. The potentiated response was followed for at least 15 min and, in some cases, up to several hours. In most animals, a number of these potentiation trials were run using various stimulus intensities for the potentiating trains.

Data analysis was performed on printed evoked potentials, each of which was a computer average of the responses to 4 consecutive test stimuli. These potentials exhibit several components corresponding to various aspects of the dentate gyrus response to afferent stimulation. The slow negative potential (population EPSP) recorded

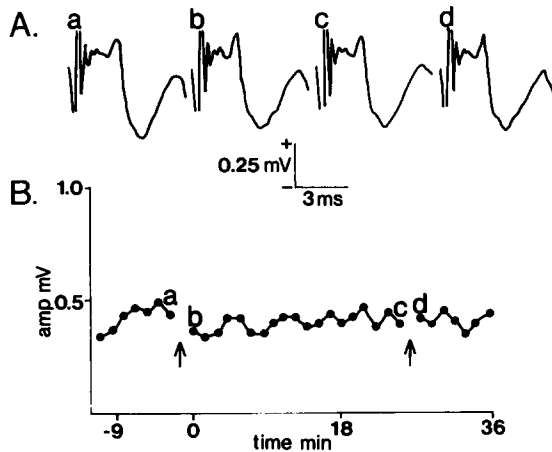


Fig. 2. Example of an LTP trial conducted on the population EPSP evoked via the small normal crossed temporodentate pathway. A: sample averaged evoked potentials recorded prior to 400 Hz conditioning (a), immediately after the first conditioning series (b), before the second conditioning series (c), and following that second 400 Hz series (d). B: plot of test response amplitude before and after 400 Hz conditioning. Points a, b, c, and d refer to the averaged evoked potentials illustrated in A. Test and conditioning stimulation in this case was 27 mA constant current.

in the dentate synaptic layer (see Fig. 1A) represents an extracellular reflection of the summed excitatory synaptic currents¹⁴ and was quantified by measuring both its initial slope and peak amplitude. In the case of the normal crossed response (see Fig. 2A) peak amplitude was measured since, because of the small size of the response, the initial slope may be contaminated by volume conducted ipsilateral responses. At the level of the dentate cell layer, the synaptic response reverses polarity to a positive potential upon which is superimposed a sharp negative going deflection (see Fig. 1A), the so-called population spike. This population spike is correlated with granule cell discharge¹ and its onset to peak amplitude was taken as measure of the number of granule cells synchronously discharged by a stimulus to the ipsilateral or lesion-induced temporodentate pathways¹⁴.

The success of each trial in producing LTP of one of these parameters was judged by comparing 4 averaged responses obtained immediately prior to delivery of a potentiating stimulus train with two similar sets of responses obtained approximately 1 min and 15 min after the train. LTP was defined as occurring when both post-train response means were significantly (*t*-test, $P < 0.05$) greater than the baseline mean.

RESULTS

The two patterns of stimulation used to induce LTP along the normal ipsilateral temporodentate pathway were found to be differentially effective. Results obtained using long low frequency (15–50 Hz) conditioning trains were inconsistent. Population spike LTP was produced in only 7/13 animals, even after repeated application of the potentiating stimulation, and potentiation of the population EPSP was observed in only 2/12 animals. As reported by Douglas⁴ replacing 6–8 single test pulses with short

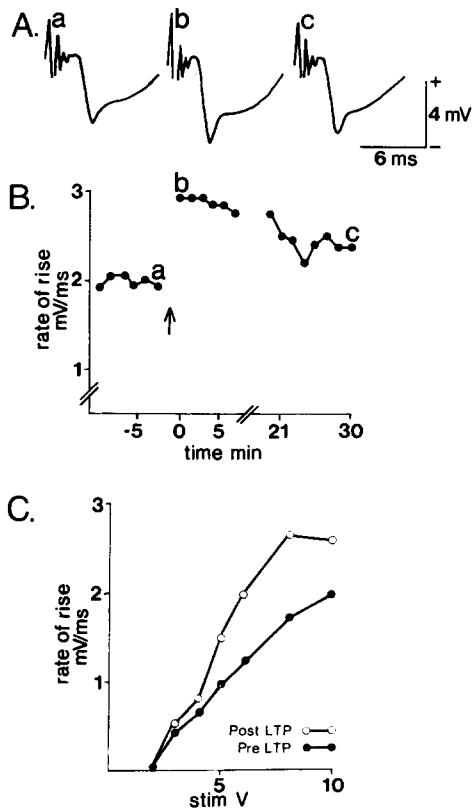


Fig. 3. LTP trial conducted on the population EPSP evoked via the lesion-induced crossed temporo-dentate pathway. A: sample averaged evoked potentials obtained prior to (a) and following (b, c) 400 Hz conditioning. Note that population EPSPs are approximately 8 times the size of those obtained via the normal crossed pathway (Fig. 2). B: LTP trial. Test stimulus and conditioning stimulation (\uparrow) were both delivered at 8 V. Points a, b, and c correspond to the evoked potentials in A. The break between points b and c represents an 11 min period during which the post-LTP input-output function (C) was taken. C: pre-LTP and post-LTP input-output functions.

bursts of 400 Hz stimulation proved to be a far more reliable means of inducing LTP. In experiments using this procedure, EPSP potentiation occurred in 9/9 animals and population spike potentiation was obtained in 8/8 animals. Since the latter method of producing LTP was much more reliable, comparisons between normal and lesion-induced crossed systems were based on this conditioning regimen.

An example of LTP of synaptic transmission in the normal ipsilateral circuit is illustrated in Fig. 1. Analogue records (Fig. 1A) clearly show that the dentate synaptic layer population EPSP increased in amplitude and rate of rise following delivery of a series of 400 Hz conditioning trains, indicating an increase in total synaptic current measured by the extracellular electrode. Likewise, the population spike simultaneously recorded at the level of the dentate cell layer increased in amplitude after delivery of the potentiating trains suggesting that a greater number of granule cells are synchronously discharged by the test shock. In this example, potentiation of the evoked responses continued with little decrement for the 28 min duration of the trial (Fig. 1B)

TABLE I

Summary of LTP data

<i>Response</i>	<i>Number of rats showing LTP[§]</i>	<i>Mean % of baseline \pm SE*</i>
Normal ipsilateral population EPSP	9/9	141 \pm 8.2 (143 \pm 7.1)
population spike	8/8	350 \pm 97
Lesion-induced crossed population EPSP	8/9	114 \pm 1.5 (122 \pm 2.6)
population spike	1/7	96 \pm 18
Normal crossed population EPSP	0/8	99 \pm 3.3

[§] Criteria for LTP were as described in Methods.

* Post-LTP response amplitudes were averaged over 15 min immediately following conditioning for each animal and compared to the average baseline response. To obtain mean % of baseline, results were averaged across animals. Results in parentheses were calculated using the maximal rate of rise of the response.

while in several other experiments potentiated responses were followed for several hours. The input-output functions obtained prior to and following LTP induction (Fig. 1C) demonstrate that potentiation involved an increase in the absolute maximum population spike and population EPSP evokable, along with a decrease in threshold for production of a population spike. No shift in the minimal stimulus required to evoke an EPSP was observed. These changes in response input-output characteristics were typical of results obtained in LTP experiments on the ipsilateral pathway.

In normal rats, stimulation of the entorhinal area or angular bundle produces, in addition to large population responses in the ipsilateral dentate gyrus, a small monosynaptic population EPSP in the contralateral dentate gyrus; however, this normal crossed component of the temporodentate projection is too small to discharge enough granule cells to elicit a population spike³⁴. Attempts to potentiate the small crossed population EPSP invariably gave the results shown in Fig. 2. Administration of 400 Hz stimulus trains in a paradigm identical to that which produced dramatic and consistent potentiation of ipsilateral dentate population EPSPs had no apparent effect on the amplitude of the crossed response. Despite repeated trials in each animal, LTP was observed in 0/8 rats in which the crossed EPSP was recorded (see Table I) although potentiation of the ipsilateral EPSP was seen in cases where this response was simultaneously recorded (for an example of such simultaneous recording, see the accompanying report, ref. 10).

Following unilateral entorhinal lesions and sprouting of crossed connections, contralateral entorhinal stimulation results in synaptic responses in the reinnervated dentate gyrus several times larger than those seen in normal animals²⁷. This pathway also gains, via sprouting, sufficient synaptic potency to monosynaptically discharge large numbers of dentate granule cells, as evidenced by a measurable population spike. In addition to these changes in electrophysiological potency, the lesion-induced crossed temporodentate pathway exhibits an increased capacity for LTP (see Table I).

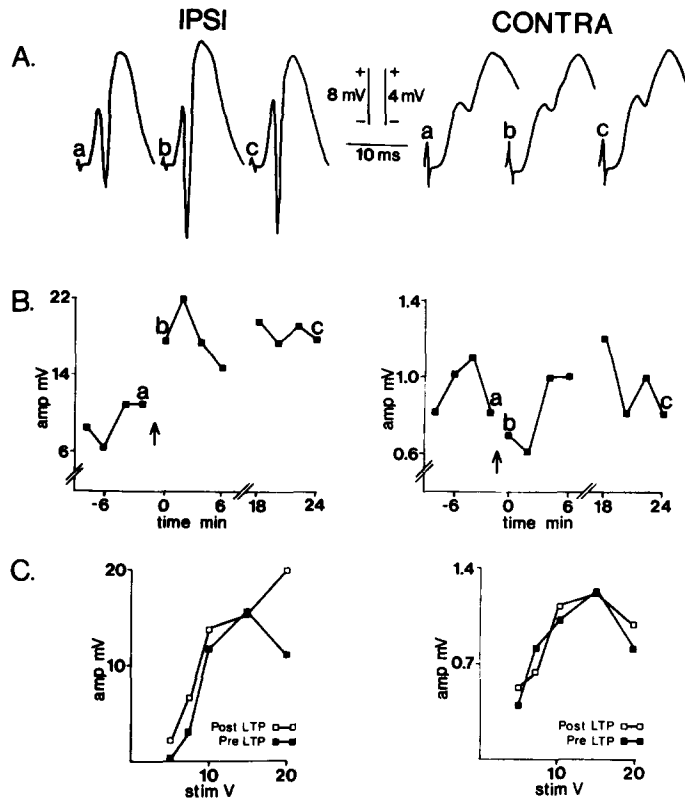


Fig. 4. Comparison of LTP of simultaneously recorded ipsilateral (left column) and lesion-induced crossed (right column) population spikes. A: sample averaged evoked potentials. Responses a, b and c were recorded prior to, immediately following, and 24 min after the conditioning stimulation, respectively. B: LTP trial on the simultaneously recorded ipsilateral and contralateral population spikes. Points a, b, and c correspond to the averaged evoked potentials above. Test and 400 Hz conditioning stimulation (\uparrow) were at 10 V intensity. The break between points b and c represents a 9 min period during which the post-LTP input-output functions were recorded. C: pre-LTP and post-LTP input-output functions.

As illustrated in Fig. 3, in an animal which had survived for at least 30 days postlesion, the population EPSP of the reinnervated dentate gyrus evoked by contralateral stimulation was capable of undergoing LTP in a manner qualitatively similar to that demonstrated in Fig. 1 for the normal ipsilateral pathway. Following conditioning of the sprouted pathway, both the amplitude and rate of rise of the evoked potential are increased (Fig. 3A). The potentiation lasts at least 30 min (Fig. 3B) although the magnitude of the potentiation declines somewhat over this time period. The input-output functions in Fig. 3C show that the EPSP response threshold is unchanged following potentiation and that the maximum response is increased. These features all resemble EPSP potentiation in the ipsilateral circuit. Similar results were observed in 8 of the 9 animals tested.

Despite consistent potentiation of the crossed population EPSP in operated animals, population spike LTP proved very difficult to obtain, and appeared in only

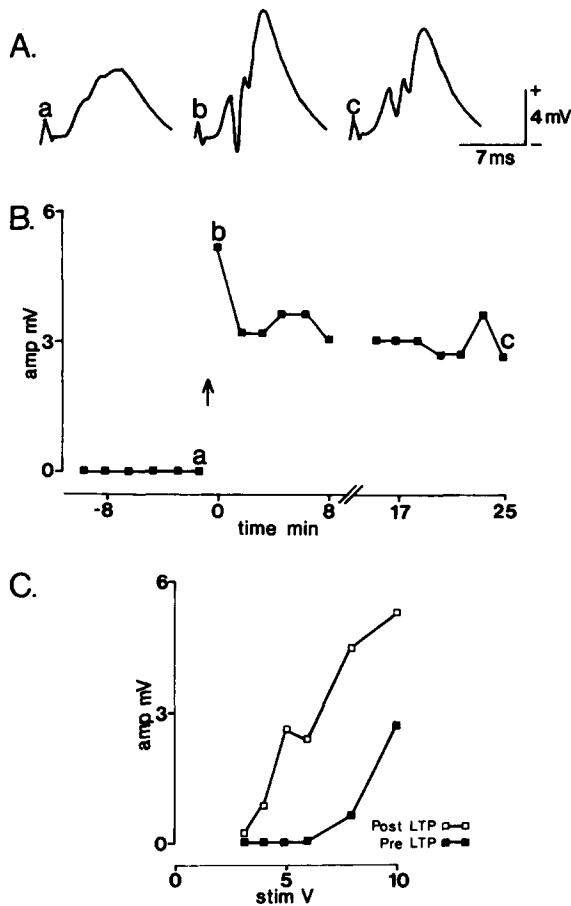


Fig. 5. LTP trial demonstrating the effect of low intensity conditioning on population spike LTP in the normal ipsilateral temporodentate circuit. A: sample averaged evoked potentials recorded before (a), immediately following (b), and 25 min after 400 Hz conditioning stimulation. B: LTP of test responses. Points a, b, and c correspond to the responses illustrated above. Conditioning stimulation (\uparrow) and test stimuli were delivered at 6 V. The break between points b and c represents an 8 min period during which the post-LTP input-output function was taken. C: pre-LTP and post-LTP input-output functions.

1/7 animals (see Table I). A typical experiment is shown in Fig. 4 in which the population spikes ipsilateral and contralateral to the stimulation were simultaneously recorded. Ipsilateral spike LTP appears normal (compare Figs. 1 and 4); however, the much smaller population spike recorded contralaterally fails to undergo potentiation even though the ipsilateral and contralateral pathways were simultaneously exposed to exactly the same stimulus patterns. A similar absence of population spike potentiation in the crossed pathway was observed in animals where the crossed EPSP exhibited clear potentiation.

One possibility which could conceivably account for an absence of population spike potentiation is the fact that the population spike evoked by the lesion-induced crossed pathway is small in comparison with that evoked via the normal ipsilateral

pathway, suggesting that fewer granule cells are activated. To examine the effect of population spike amplitude on the extent of its potentiation, we conducted LTP trials on the normal ipsilateral circuit in which low test and conditioning stimulus intensities were used to produce population spikes with amplitudes comparable to those found in the lesion-induced crossed temporodentate pathway. An example is illustrated in Fig. 5. Prior to potentiation, the ipsilateral population spike can be seen as a slight deflection on the rising phase of the slow positive potential (Fig. 5A). Following 400 Hz conditioning at this stimulus intensity, this ipsilateral population spike underwent marked potentiation. Thus, the fact that only a small population spike is evoked by the lesion-induced crossed pathway cannot account for the absence of population spike potentiation.

The magnitude of the potentiation produced was subject to some variability and appears to be affected by such factors as test stimulus intensity and conditioning stimulus intensity, parameters which are difficult to match across subjects. As is evident in Table I, however, this variability was relatively minor in comparison to the extent of the potentiation under our testing regimen. In addition, this table points out the striking difference between population spike LTP in the normal and reinnervated dentate gyrus. Over a 15 min period immediately following conditioning, the normal ipsilateral spike averaged 350% of its pre-LTP baseline while the population spike evoked via the lesion-induced crossed pathway was nearly unchanged or even slightly depressed following conditioning stimulation, averaging 96% of baseline. However, potentiation of the synaptic potentials associated with both these responses was apparent. When quantified in terms of initial rate of rise, the potentiated ipsilateral population EPSP averaged 143% and the lesion-induced crossed EPSP averaged 122% of their respective pre-LTP baselines. To permit direct comparison of this population EPSP potentiation with the effects of conditioning the small normal crossed EPSP, response amplitude was also measured. While the size of the normal crossed EPSP seemed little affected following conditioning (99% of baseline) the post-LTP amplitude of the normal ipsilateral and lesion-induced crossed responses increased in parallel with their rates of rise, averaging 141% and 114% of baseline, respectively.

DISCUSSION

Two main findings emerge from these experiments. First, the small population EPSP evoked in the dentate gyrus of normal animals by contralateral entorhinal stimulation could not be induced to potentiate using a stimulation paradigm similar to that which produced consistent LTP of ipsilateral synaptic responses. However, the crossed pathway which had increased its synaptic power as a consequence of sprouting exhibited LTP of the population EPSP which was similar to that of the normal ipsilateral pathway. A second chief finding of this study was that even though this lesion-induced pathway is anatomically homologous, except for its laterality, to the normal ipsilateral temporodentate projection, it may not exactly reproduce or restore all the functional properties of the ablated ipsilateral circuitry. Specifically, although

LTP of cell discharge (population spike) was very prominent in the ipsilateral circuit in normal animals, little evidence was found to suggest that population spike LTP occurs in the re-innervated dentate gyrus despite a distinct potentiation of synaptic drive.

The emergence, following sprouting, of LTP capability in a previously non-potentiating pathway could result from a variety of alterations in the crossed temporodentate circuitry. Sprouting might, for example, produce presynaptic changes in the physiology of proliferating terminals or possibly changes in the postsynaptic structures they come to innervate. However, a simple and attractive explanation for the sprouting related increase in LTP capacity of the crossed temporodentate pathway is suggested by the observations of Levy and Steward¹⁰. They found that LTP of the small normal crossed synaptic response could be induced via a stimulation regimen in which conditioning bursts were delivered simultaneously to both the contralateral and ipsilateral temporodentate pathways. On the basis of this finding and because normal ipsilaterally evoked population EPSPs fail to potentiate in trials using very low intensity stimuli which activate only a small population of synaptic terminals (ref. 6, our own unpublished observations), it has been hypothesized that LTP might be a cooperative phenomenon which requires a minimum number of co-active synapses^{6,10}. Although the exact mechanism of LTP remains uncertain, this hypothesis of cooperativity can explain the emergence of LTP capability in the lesion-induced crossed pathway. Since sprouting involves large increases in the number of crossed temporodentate terminals, the number of synapses co-activated by stimulation of this pathway may increase following sprouting above some critical number required for LTP induction.

Our second main experimental finding, i.e. the failure to record consistent population spike LTP in the reinnervated dentate gyrus, while finding distinct potentiation of synaptic drive, is remarkably similar to earlier results concerning paired pulse potentiation in this system²⁹, and is somewhat enigmatic. It is conceivable that the lesion-induced crossed projection lacks sufficient synaptic power or sufficient EPSP potentiation to sustain potentiation of granule cell discharge. However, several lines of evidence run counter to this notion. Stimulation of this pathway evokes clear population spikes indicating that the lesion-induced connections are capable of driving granule cells. Although the average magnitude of EPSP potentiation was somewhat less in the lesion-induced crossed circuit than in the ipsilateral pathway (see Table I) we observed several cases in which distinct ipsilateral spike LTP was obtained even though the magnitude of ipsilateral EPSP potentiation was comparable to that seen in the lesion-induced crossed circuit. In addition, as illustrated in Fig. 5, ipsilateral spike potentiation may be obtained even when the conditioning stimulation is at an intensity initially evoking only a small population spike. Thus, we feel it unlikely that a lack of sufficient synaptic potency in the lesion-induced crossed pathway can account for the absence of population spike LTP.

Granule cell discharge in the reinnervated dentate gyrus may depend, however, upon a number of imposed secondary factors in addition to synaptic depolarization via crossed entorhinal afferents and these secondary factors may be responsible for the absence of short term or long term potentiation of the population spike. For example,

contralateral entorhinal stimulation activates multisynaptic circuits in addition to the direct crossed pathway²⁴. Because the lesion-induced population spike is somewhat delayed in time with respect to the ipsilateral spike (see Fig. 4), cell discharge in the crossed system may fall within a time range which could subject it to interaction with these multisynaptic excitatory inputs. In addition, intrinsic inhibitory circuits could prevent the expression of population spike LTP. Recent observations on the trajectory of the lesion-induced crossed projection demonstrates that the reinnervating fibers enter the dentate gyrus predominantly at its rostral-medial tip, and then project caudally and laterally²³. The normal ipsilateral projections, on the other hand, enter the dentate gyrus from the caudal end, and project rostrally in lamellae. Axons of the intrinsic inhibitory interneurons (basket cells) extend for distances of up to 1 mm in the rostrocaudal axis of the dentate and 0.5 mm in the mediolateral direction³¹. It is possible that the intrinsic inhibitory circuits are organized in such a way that activation of the granule cells in a caudorostral sequence, as occurs in the normal ipsilateral entorhinal projection system, is critical for the expression of population spike LTP. Because the densest innervation by the lesion-induced crossed pathway is in the rostral dentate gyrus, stimulation of this projection may produce early discharge of granule cells in this region and early activation of basket cells which project caudally, thus producing feed-forward inhibition to more caudal regions. Depending on the timing between this feed-forward inhibition, and subsequent activation by the caudally projecting crossed temporodentate fibers, the inhibitory inputs may prevent the expression of population spike LTP by inhibiting the population spike.

Finally, it is possible that, following LTP, the increased synaptic drive in the reinnervated dentate gyrus does produce increased granule cell discharge which goes undetected by our methods. If, for example, the increased granule cell firing was less synchronous after potentiation, then this potentiated but non-synchronous firing would not necessarily be reflected in the population spike amplitude. Indeed, although the crossed population spike is certainly associated with cell firing²⁴, it remains to be established that the amplitude of this crossed spike is as well correlated with the number of cells discharged as is the normal ipsilaterally evoked spike. Final determination of the reasons for the difference between spike potentiation in the normal ipsilateral and lesion-induced crossed connections awaits more detailed quantitative studies on the relationship between EPSP and spike potentiation and on single cell responses.

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REFERENCES

- 1 Andersen, P., Bliss, T. and Skrede, K., Unit analysis of hippocampal population spikes, *Exp. Brain Res.*, 13 (1971) 208-221.
- 2 Bliss, T. and Lomo, T., Long-lasting potentiation of synaptic transmission in the dentate area of

- the anesthetized rabbit following stimulation of the perforant path, *J. Physiol. (Lond.)*, 232 (1973) 331–356.
- 3 Bliss, T. and Gardner-Medwin, A., Long-lasting potentiation of synaptic transmission in the dentate area of the unanesthetized rabbit following stimulation of the perforant path, *J. Physiol. (Lond.)*, 232 (1973) 357–374.
 - 4 Douglas, R., Long-lasting synaptic potentiation in the rat dentate gyrus following brief high frequency stimulation, *Brain Research*, 126 (1977) 361–365.
 - 5 Douglas, R. and Goddard, G., Long-term potentiation of the perforant path-granule cell synapse in the rat hippocampus, *Brain Research*, 86 (1975) 205–215.
 - 6 Douglas, R. and McNaughton, B., Enhancement of synaptic responses to stimulation of the perforant path is dependent on the numbers of fibers activated, *Society for Neuroscience, 7th Annual Meeting, 1977*, Abstract.
 - 7 Goldowitz, D., White, W., Steward, O., Cotman, C. and Lynch, G., Anatomical evidence for a projection from the entorhinal cortex to the contralateral dentate gyrus of the rat, *Exp. Neurol.*, 47 (1975) 433–441.
 - 8 Goodman, D. C. and Horel, J. A., Sprouting of optic tract projections in the brain stem of the rat, *J. comp. Neurol.*, 127 (1966) 71–88.
 - 9 Harris, E., Lasher, S. and Steward, O., Habituation-like decrements in transmission along the normal and lesion-induced temporo-dentate pathways in the rat, *Brain Research*, 151 (1978) 623–631.
 - 10 Levy, W. and Steward, O., Synapses as associative memory elements in the hippocampal formation, *Brain Research*, 175 (1979) 233–245.
 - 11 Liu, C. N. and Chambers, W. W., Intraspinal sprouting of dorsal root axons, *Arch. Neurol. Psychiat.*, 79 (1958) 46–61.
 - 12 Loesche, J. and Steward, O., Behavioral correlates of denervation and reinnervation of the hippocampal formation of the rat: recovery of alternation performance following unilateral entorhinal cortical lesions, *Brain Res. Bull.*, 2 (1977) 1–9.
 - 13 Lømo, T., Frequency potentiation of excitatory synaptic activity in the dentate area of the hippocampal formation, *Acta physiol. scand.*, Suppl. 277, 66 (1966) 128.
 - 14 Lømo, T., Patterns of activation in a monosynaptic cortical pathway: the perforant path input to the dentate area of the hippocampal formation, *Exp. Brain Res.*, 12 (1971) 18–45.
 - 15 Lømo, T., Potentiation of monosynaptic EPSPs in the perforant path-dentate granule cell synapse, *Exp. Brain Res.*, 12 (1971) 46–63.
 - 16 Lynch, G., Matthews, D., Mosko, S., Parks, T. and Cotman, C., Induced acetylcholinesterase-rich layer in rat dentate gyrus following entorhinal lesions, *Brain Research*, 42 (1972) 311–318.
 - 17 Lynch, G., Stanfield, B. and Cotman, C. W., Developmental differences in postlesion axonal growth in the hippocampus, *Brain Research*, 59 (1973) 155–168.
 - 18 McCouch, G. P., Austin, C. M., Liu, C. N. and Liu, C. Y., Sprouting as a cause of spasticity, *J. Neurophysiol.*, 21 (1958) 205–216.
 - 19 Nadler, J., Cotman, C. and Lynch, G., Biochemical plasticity of short-axon interneurons: Increased glutamate decarboxylase activity in the denervated area of rat dentate gyrus following entorhinal lesion, *Exp. Neurol.*, 45 (1974) 403–413.
 - 20 Nakamura, Y., Mizuno, N., Konishi, A. and Sato, M., Synaptic reorganization of the red nucleus after chronic deafferentation from cerebellorubral fibers: an electron microscopic study in the cat, *Brain Research*, 82 (1974) 298–301.
 - 21 Raisman, G., Neuronal plasticity in the septal nuclei of the adult rat, *Brain Research*, 14 (1969) 25–48.
 - 22 Stenevi, U., Björklund, A. and Moore, R. Y., Morphological plasticity of central adrenergic neurons, *Brain Behav. Evol.*, 8 (1973) 110–134.
 - 23 Steward, O., Trajectory of contralateral entorhinal axons which reinnervate the fascia dentata of the rat following ipsilateral entorhinal lesions, *Brain Research*, in press.
 - 24 Steward, O., Cotman, C. W. and Lynch, G. S., Re-establishment of electrophysiologically functional cortical input to the dentate gyrus deafferented by ipsilateral entorhinal lesions: innervation by the contralateral entorhinal cortex, *Exp. Brain Res.*, 18 (1973) 396–414.
 - 25 Steward, O., Cotman, C. W. and Lynch, G. S., Growth of a new fiber projection in the brain of adult rats: re-innervation of the dentate gyrus by the contralateral entorhinal cortex following ipsilateral entorhinal lesions, *Exp. Brain Res.*, 20 (1974) 45–66.
 - 26 Steward, O., Cotman, C. and Lynch, G., Selectivity in the pattern of new synapse formation with

- denervated granule cells, *Fourth Annual Meeting of the Society for Neuroscience, St. Louis, Missouri, 1974*, Abstract.
- 27 Steward, O., Cotman, C. and Lynch, G., A quantitative autoradiographic and electrophysiological study of the reinnervation of the dentate gyrus by the contralateral entorhinal cortex following ipsilateral entorhinal lesions, *Brain Research*, 114 (1976) 181-200.
 - 28 Steward, O. and Vinsant, S. L., Collateral projections of cells in the surviving entorhinal area which reinnervate the dentate gyrus of the rat following unilateral entorhinal lesions, *Brain Research*, 149 (1978) 216-222.
 - 29 Steward, O., White, W., Cotman, C. and Lynch, G., Potentiation of excitatory synaptic transmission in the normal and reinnervated dentate gyrus of the rat, *Exp. Brain Res.*, 26 (1976) 423-441.
 - 30 Steward, O., White, W. F. and Cotman, C. W., Potentiation of the excitatory synaptic action of commissural, associational and entorhinal afferents to dentate granule cells, *Brain Research*, 147 (1977) 551-560.
 - 31 Struble, R. G., Desmond, N. L. and Levy, W. B., Anatomical evidence for interlamellar inhibition in the fascia dentata, *Brain Research*, 152 (1978) 580-585.
 - 32 Teyler, T. and Alger, B., Monosynaptic habituation in the vertebrate forebrain: the dentate gyrus examined in vitro, *Brain Research*, 115 (1976) 413-425.
 - 33 Westrum, L. E., Axonal patterns in olfactory cortex after olfactory bulb removal in newborn rats, *Exp. Neurol.*, 47 (1975) 442-447.
 - 34 White, W., Goldowitz, D., Lynch, G. and Cotman, C., Electrophysiological analysis of the projection from the contralateral entorhinal cortex to the dentate gyrus in normal rats, *Brain Research*, 114 (1976) 201-209.
 - 35 Wilson, R. and Steward, O., Long-term potentiation in the lesion-induced crossed temporo-dentate pathway of the rat, *Society for Neuroscience, 8th Annual Meeting, St. Louis, Missouri, 1978*, Abstract.
 - 36 Zimmer, J., Extended commissural and ipsilateral projections in postnatally deentorhinated hippocampus and fascia dentata demonstrated in rats by silver impregnation, *Brain Research*, 64 (1973) 293-311.
 - 37 Zimmer, J., Changes in the Timm sulfide silver staining pattern of the rat hippocampus and fascia dentata following early postnatal deafferentation, *Brain Research*, 64 (1973) 313-326.
 - 38 Zimmer, J. and Hjorth-Simonsen, A., Crossed pathways from the entorhinal area to the fascia dentata. II. Provokable in rats, *J. comp. Neurol.*, 161 (1975) 71-102.