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BRIEF REPORT

An Experimental Test of Diaschisis[1]

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The diaschisis theory of recovery of function was directly tested for the first time. Using the dentate gyrus in adult rats as the model system, extracellular field potentials elicited by commissural stimulation were monitored in both acute and chronic animal preparations before and from 0.5 hr to 11 days following the lesion. The lesion resulted in the loss of the commissurally elicited long-latency potential but did not disrupt the short-latency monosynaptic potential. No changes in latency, amplitude, form, or stimulus threshold in the monosynaptic potential could be detected.

In 1910 von Monakow proposed that the loss of behavioral functions seen after damage to the brain was due to two factors: (1) the destruction of tissue involved in the lesion, and (2) a depression of function or loss of responsiveness in those brain regions connected to the damaged area. This second effect von Monakow termed "diaschisis." von Monakow envisioned that the areas connected to the damaged region go into a state of shock: "In the case of diaschisis the ability to respond to stimuli of the central element giving that response becomes impaired, abolished or refractory" (von Monakow, 1969, p. 28). He hypothesized that diaschisis appears suddenly, dissipates with time, and as it dissipates functions reappear. von Monakow proposed that although diaschisis might not always occur, it is dependent upon the extent of the insult and is enhanced by other concurrent disorders (e.g., latent circulatory abnormalities). This model of recovery from brain damage has been widely discussed since von Monakow's paper (Lynch *et al.*, 1976) but apparently has never received a direct experimental test in the brain. This was the purpose of the study described in this communication.

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We selected the dentate gyrus of the hippocampal formation of the adult rat as a model system in which to examine the diaschisis hypothesis. The arrangement of cells and afferents makes this region of the brain particularly suitable for such an experimental test. The granule cells of the dentate gyrus receive terminals from the entorhinal cortex on the outer two-thirds of their dendrites (Raisman *et al.*, 1965; Hjorth-Simonsen and Jeune, 1972) and afferents from the associational and commissural systems (which originate in the ipsilateral and contralateral hippocampus, respectively) on the remaining inner one-third of their dendrites (Blackstad, 1956; Raisman *et al.*, 1965; Zimmer, 1971; Gottlieb and Cowan, 1972). The diaschisis hypothesis would predict that removal of one of these inputs would make the granule cells less responsive to the remaining afferents. Therefore, we destroyed the entorhinal cortex which causes the loss of the great majority of the terminals in the outer dendritic field (unpublished data from this laboratory) and measured the extracellular potentials and unit discharges of the granule cells to monosynaptic stimulation of the commissural system.

Male albino rats, anesthetized with urethane (800 mg)/or Nembutal (35 mg/kg), were used for all experiments in the arrangement illustrated in Fig. 1. A low resistance (2-4 Mohm) 2 M NaCl-filled micropipet recording electrode (tip, 1-3 μm) was monitored into the dorsal aspect of the dentate gyrus. An etched tungsten stimulating electrode (tip, 10 μm) was placed into field CA3 of the contralateral hippocampus.

In three additional animals a 30-gauge insulated stainless steel stimulating electrode was permanently implanted in field CA3 of the hippocampus, and a guide cannula (1.5 mm i.d.) for the microelectrode was affixed to the

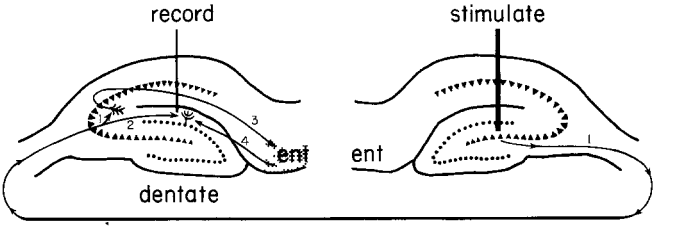

Fig. 1. A schematic representation of the electrode locations and neuronal systems utilized in this experiment. The numbers refer to the sequence of events initiated by stimulation of field CA3 contralateral to a recording electrode in the dentate gyrus: (1) stimulation of the commissural system, (2) synaptic activation of the regio inferior pyramidal cells and inner molecular layer of the dentate gyrus, (3) driving of the entorhinal cortex via the hippocampal-entorhinal pathway (Hjorth-Simonsen, 1972), and (4) depolarization of the outer molecular layer via the perforant pathway. Note that the dentate gyrus receives two inputs, one monosynaptic, the second polysynaptic, and that the second potential is eliminated by the entorhinal lesion (stripes).

skull above the contralateral hippocampus. A fourth rat was prepared in a manner similar to the other chronic animals except that a chronic microdrive unit was attached for recording purposes. This allowed an even more precise monitoring of dendritic areas in the dentate gyrus along the same electrode track.

Following the initial collection of data, the entorhinal cortex ipsilateral to the cannula was electrolytically destroyed. Upon termination of the recording sessions, the microelectrode was removed and the cannula was filled with mineral oil and capped. The animal was then allowed to recover, and after variable periods was again anethesized, and the microelectrode was reintroduced to the dentate gyrus through the cannula guide. With this arrangement it was possible to test for shock at the same stimulating and recording loci immediately after the entorhinal lesion and after extended periods of postlesion recovery.

At the conclusion of the experiments a small quantity of horseradish peroxidase (West *et al.*, 1975a) was ejected from the recording electrode to mark its position. Entorhinal lesions were verified using standard histological reconstruction procedures.

Electrical stimulation of field CA3 produced a short-latency positive potential (2-4 msec) in the granule-cell layer of the contralateral dentate gyrus which reflects monosynaptic activation via commissural fibers (Deadwyler *et al.*, 1975a). When the microelectrode was raised into the zone immediately above the granule cells (in the region of termination of the commissural fibers) the potential reversed and became negative. This negative potential is the extracellular manifestation of summed excitatory postsynaptic potentials initiated by activation of afferent fibers (Lømo, 1971; Deadwyler, *et al.*, 1975a).

At higher stimulation intensities or frequencies a second longer latency (20-25 msec) potential was seen (Fig. 2B). This "late" potential was positive in the granule-cell layer but negative in the outer two-thirds of the molecular layer, where the entorhinal endings are found (Raisman *et al.*, 1965; Hjorth-Simonsen and Jeune, 1972). It results from the polysynaptic activation of the ipsilateral entorhinal cortex (Deadwyler *et al.*, 1975b). Figure 1 summarizes the probable pathway involved. After the electrodes were correctly positioned, the relationship of intensity of commissural stimulation to the short-latency monosynaptic response of the dentate gyrus was established. Measurements of field potentials were taken at the granule-cell layer and immediately above it in the zone of commissural endings. The entorhinal cortex was then destroyed and the measurements of the commissural potentials were again obtained.

The entorhinal lesion had no effect on the latency, wave form, or magnitude of the monosynaptic commissural potential. Neither did it change the distribution of these potentials within the dentate gyrus. We have tested for changes in the commisural response over periods of up to 6 hr after the

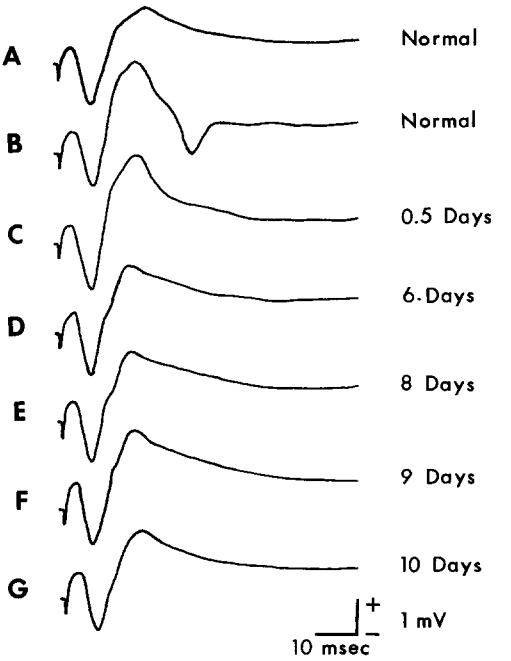

Fig. 2. Maximum negative extracellular commissural field potentials recorded 100-150 μm above the granule-cell layer of the dentate gyrus. Eight potentials were taken and averaged on a Nuclear Chicago data retrieval computer and printed out on an x-y plotter. (A) Prelesion commissural response below the threshold for eliciting the late potential. (B) Prelesion commissural response eliciting the late potential (1.2/sec stimulation frequency). (C) Postlesion commissural response recorded 12 hr after the lesion. (D) Postlesion commissural response recorded 6 days after the lesion (E) Post lesion commissural response recorded 8 days after the lesion (F) Postlesion response recorded 9 days after the lesion. (G) Postlesion commissural response recorded 10 days after the lesion. Stimulation voltage was 3.5 V in each example. Stimulation frequency was 0.7/sec, except where noted.

entorhinal lesions in six acute preparations and have found no evidence of change in the commissural potentials or unit discharges in the dentate gyrus. Although the entorhinal lesion has no effect on the initial response to commissural stimulation, it completely abolished the longer latency entorhinal mediated late potential (Fig. 2).

Tests conducted at longer intervals after the lesion in three chronic rats also indicated no detectable differences in the short-latency commissural response.

Table 1 shows the amplitude of both the negative and positive commissural field potentials recorded from the chronic animals at various time

TABLE 1

Comparison of Amplitude of Commissural Potentials in the Granule-Cell Layer and in the Commissural Synaptic Field 100-150 μm Above the Granule-Cell Layer[a]

	Chronic animals[b]																	
	C1			C2			C3						C4					
Postlesion time (days)	N[c]	1	4	N	0.1	2	N	0.1	3	4	7	8	N	0.5	6	8	9	10
Cell-layer response (+)	2.0	2.0	2.0	3.0	3.1	2.9	1.2	1.2	1.3	–	1.4	1.3	2.4	2.4	2.5	2.3	2.5	2.4
Commissural synaptic field (Max, –)	1.5	1.5	1.5	2.0	2.0	2.0	1.0	1.0	1.0	–	1.1	1.0	1.6	1.7	1.7	1.7	1.8	1.7

[a]Data were measured from eight averaged traces taken from chronically implanted rats, before and 0.1 or more days following a unilateral entorhinal lesion.

[b]These animals were all experimental animals.

[c]N = normal response prior to lesion.

points following the lesion. Neither the earlier commissural negativity nor positivity was affected. In one instance a decrease in the amplitude of the negative evoked potential was observed at 4 days following the lesion, but decreases were observed throughout other regions of the hippocampus, indicating a general depression of hippocampal electrical activity. During subsequent recording sessions the potentials again appeared normal.

The rat fitted with the chronic microdrive was tested before the lesion was made and at 0.5, 8, 9, and 10 days afterward. Figure 2 illustrates the remarkable consistency in the commissurally elicited dentate potentials over this period of time. Normal potentials were recorded both with and without the late potential. Using the same stimulus voltage, the later negative potential could easily be recruited by raising the stimulus frequency from 0.7/ to 1.2/sec (Fig. 2B). The change in frequency had no effect on the amplitude or shape of the monosynaptic potential. Although all postlesion potentials shown in Fig. 2 were averaged from a 0.7/sec stimulation, during each subsequent recording session several higher intensities and rates of stimulation were employed in unsuccessful attempts to elicit the late potential.

These results demonstrate that removal of the massive entorhinal projections to the granule cells causes no appreciable change in their responsiveness to a second convergent afferent input via the commissural pathway. As such, the findings provide the first rigorous test of the diaschisis argument in the brain and clearly do not support that hypothesis. With the reservation that our findings may not generalize to all brain systems we suggest that "shock" effects are not to be found at the projection sites of a lesioned structure. This of course does not preclude their occurrence at areas surrounding or encroached upon by the lesion (Glassman, 1971).

The diaschisis argument has been proposed as an explanation for behavioral disruptions following brain damage, as well as their subsequent recovery. The findings presented here are in disagreement with such explanations and indicate that convergent afferent pathways remain functional when alternative systems are removed or destroyed. Recovery from brain damage must therefore be determined by other factors. It is noteworthy in this regard that lesions of the type used in this study produce a considerable degree of axon sprouting in the dentate gyrus (Lynch *et al.*, 1972; Lynch, *et al.*, 1973b; Steward *et al.* 1974), some of which recently has been shown to result in the formation of new functional terminals as soon as 9 days after the lesion (Lynch *et al.*, 1973a; Steward *et al.*, 1974; West *et al.* 1975b).

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