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Feedforward excitation of the hippocampus by afferents from the entorhinal cortex: Redefinition of the role of the trisynaptic pathway

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ABSTRACT **For the past 3 decades, functional characterizations of the hippocampus have emphasized its intrinsic trisynaptic circuitry, which consists of successive excitatory projections from the entorhinal cortex to the dentate gyrus, from granule cells of the dentate to the CA3/4 pyramidal cell region, and from CA3/4 to the CA1/2 pyramidal cell region. Despite unequivocal anatomical evidence for a monosynaptic projection from entorhinal to CA3 and CA1/2, few *in vivo* electrophysiological studies of the direct pathway have been reported. In the experiments presented here, we stimulated axons of entorhinal cortical neurons *in vivo* and recorded evoked single unit and population spike responses in the dentate, CA3, and CA1 of hippocampus, to determine if pyramidal cells are driven primarily via the monosynaptic or trisynaptic pathways. Our results show that neurons within the three subfields of the hippocampus discharge simultaneously in response to input from a given subpopulation of entorhinal cortical neurons and that the initial monosynaptic excitation of pyramidal cells then is followed by weaker excitatory volleys transmitted through the trisynaptic pathway. In addition, we found that responses of CA3 pyramidal cells often precede those of dentate granule cells and that excitation of CA3 and CA1 pyramidal cells can occur in the absence of granule cell excitation. In total, these results argue for a different conceptualization of the functional organization of the hippocampus with respect to the propagation of activity through its intrinsic pathways: input from the entorhinal cortex initiates a two-phase feedforward excitation of pyramidal cells, with the dentate gyrus providing feedforward excitation of CA3, and with both the dentate and CA3 providing feedforward excitation of CA1.**

The hippocampus is composed of three major subdivisions: the dentate gyrus and the CA3/4 and CA1/2 pyramidal cell regions (1). Connectivity between the three cell fields is unidirectional, with granule cells of the dentate gyrus projecting to the CA3/4 pyramidal neurons, which in turn project to CA1/2 pyramidal cells (2). Excitatory perforant path fibers arising from the entorhinal cortex are the major afferents to the dentate (3, 4), and numerous studies have demonstrated that activation of the perforant path can initiate a sequential excitation of dentate granule, CA3/4 pyramidal, and CA1/2 pyramidal cell populations (5, 6). Serial propagation through this "trisynaptic pathway" has become regarded as the fundamental characteristic of intrinsic hippocampal physiology (7).

In contrast to physiological evidence for the trisynaptic pathway, results from anatomical investigations consistently have shown that the entorhinal cortex innervates each of the dentate, CA3, and CA1/2 regions (8), suggesting simultaneous rather than sequential excitation of the three intrinsic hippocampal cell groups (see Fig. 1). Although evidence for the functional viability of monosynaptic entorhinal input to pyramidal neurons has been provided (9–11), the relative strengths of the monosynaptic and trisynaptic pathways have gone untested. At least one investigation has questioned the sufficiency of monosynaptic entorhinal input for suprathreshold activation of pyramidal neurons (5). Other studies using the *in vitro* hippocampal slice have examined pyramidal cell responses to electrical stimulation of monosynaptic afferents within the dendritic region containing terminals of entorhinal axons (12). The entorhinal pathway cannot be activated selectively in an *in vitro* preparation, however, because afferents from other brain regions terminate within the same dendritic zone (13–15). More importantly, it is not possible to establish with an *in vitro* preparation if a given subpopulation of hippocampal pyramidal neurons receives entorhinal input primarily via monosynaptic or multisynaptic pathways. Thus, the extent to which the trisynaptic pathway represents a fundamental constraint on multisynaptic transmission through the hippocampus remains to be determined. In the experiments reported here, we used electrophysiological methods to compare the latency and strength of entorhinal input to CA3 and CA1 pyramidal neurons with the latency and strength of input to dentate granule cells from the same population of entorhinal fibers.

MATERIALS AND METHODS

Male New Zealand White rabbits ($n = 45$) were anesthetized continuously with halothane. Bipolar stimulating electrodes were positioned stereotaxically into one or two of the following: (*i*) perforant path fibers of the angular bundle, (*ii*) the ipsilateral stratum radiatum of CA3 or CA1, (*iii*) the hilus ipsilateral to the perforant path stimulating electrode, (*iv*) the hilus contralateral to the perforant path stimulating electrode. Stimulation impulses (0.1–0.2 ms) were delivered by using constant low frequencies (0.2 Hz or less); pairs and triplets of impulses with interimpulse intervals that varied from 10 to 200 ms; and trains of 10–20 impulses with interimpulse intervals corresponding to 5–200 Hz.

Extracellular recording electrodes (insulated stainless steel) had tip impedances of 1–2 MΩ when tested using 135 Hz *in vitro*. Recording electrodes were positioned stereotaxically throughout the dorsal hippocampus. Recording and stimulation sites were verified by a Prussian blue reaction for iron deposits. In some experiments, the selective $GABA_A$ agonist muscimol (500 μM) was delivered with a micropressure ejection system (15-ms impulses; 5–15 psi; 1 psi = 6.9 kPa) simultaneously during recording. Evoked field potentials were band-pass filtered using low- and high-frequency limits of 10 Hz and 10 kHz, respectively. Unitary spike

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Abbreviation: EPSP, excitatory postsynaptic potential.

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events evoked from single cells were differentiated from field potentials by using low- and high-frequency limits of 100–1000 Hz and 6 kHz, respectively.

RESULTS

Multisynaptic Excitation of CA3 and CA1 Pyramidal Neurons Via the Trisynaptic Pathway. Stimulation of perforant path fibers resulted in the sequential excitation of dentate granule, CA3 pyramidal, and CA1 pyramidal cells characteristic of the trisynaptic pathway. Latencies to population and single cell responses were progressively longer within each of the three hippocampal subfields: 4–6 ms for granule cells, 9–13 ms for CA3 neurons, and 16–21 ms for CA1 cells. Responses of granule cells satisfied all established criteria (3, 4) for monosynaptic activation (Fig. 1*B*). The longer latency excitations of CA3 and CA1 neurons were consistent with multisynaptic activation, as they did not follow more than the first few impulses of trains of continuous stimulation delivered at frequencies of >25 Hz. Latencies of pyramidal cell discharge also were consistent with the cumulative monosynaptic latencies for each of the individual pathways comprising the trisynaptic circuit: 4–6 ms for perforant pathway input to granule cells, 4–8 ms for activation of CA3 by mossy fiber stimulation, and 4–6 ms for responses of CA1 cells evoked by Schaffer collateral stimulation. These observations are consistent with previous characterizations of a sequential excitation of dentate, CA3, and CA1 due to the serial organization of connectivity between the three intrinsic hippocampal subfields (7, 16).

Monosynaptic Excitation of CA3 and CA1 Pyramidal Neurons by Entorhinal Afferents. In addition to responses characteristic of multisynaptic activation, excitations of CA3 and CA1 pyramidal cells were routinely observed to occur with latencies of 4–7 ms (Fig. 2 *A* and *B*), consistent with monosynaptic input from the direct entorhinal projection. This interpretation was supported by several findings. Among those are the results of laminar analyses, in which a recording electrode was lowered progressively from the cell body layer of CA1 to the cell body layer of CA3, parallel to the dendritic axes, during low-frequency stimulation of the angular bundle. When the recording electrode was located in the cell body layer of CA1, stimulation evoked a short-latency positive-going field potential—i.e., a population excitatory postsynaptic potential (EPSP) consistent with a current sink generated by synaptic input terminating in the apical dendrites (3, 4). If sufficient stimulation current was used, a negative-going population spike was superimposed on the population EPSP; the presence of evoked action potentials with latencies corresponding to that of the negative wave confirmed its interpretation as a population spike (4, 17). When the recording electrode was moved into the apical dendritic region, the population EPSP reversed in polarity (without a change in latency) to become negative going, indicating its generation in the apical dendrites. Increasing stimulation intensity resulted in greater amplitude and onset slope of the population EPSP without decreasing onset latency, supporting an interpretation of the negativity as a dendritic response to monosynaptic input.

The population EPSP reached maximum amplitude in the distal apical dendritic regions of CA1 and CA3, in association with the appearance of presynaptic fiber volleys (Fig. 2*C*). When localized histologically, this dendritic region corresponded to stratum lacunosum-moleculare, the site for termination of entorhinal afferents as indicated by anatomical analyses (1, 8).

Dissociation of Antidromic and Orthodromic Pyramidal Cell Responses. The entorhinal cortex and pyramidal cell regions

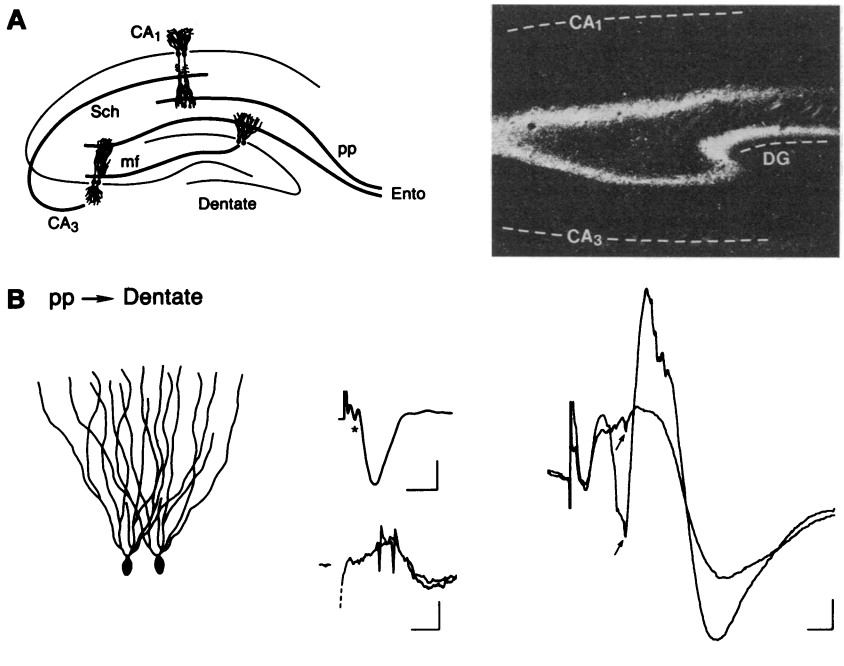

FIG. 1. (*A*) (*Left*) Schematic representation of the anatomical organization of major subfields of the hippocampus (dentate, CA1, CA3) and their relationship to afferents from the entorhinal cortex. pp, Perforant path; mf, mossy fibers; Sch, Schaffer collaterals; Ento, entorhinal cortex. (*Right*) Dark-field photomicrograph of entorhinal afferents to the stratum moleculare of the dentate gyrus (DG) and to the stratum lacunosum-moleculare of the CA3 and CA1 pyramidal cell fields of the rabbit hippocampus labeled after an injection of wheat germ agglutinin–horseradish peroxidase (2%; vol, 60 nl) into the medial entorhinal cortex. (*B*) Typical single unit and population responses of dentate granule cells evoked by stimulation of afferents from the entorhinal cortex. (*Left*) Schematic of granule cells found in the dentate gyrus. (*Upper Middle*) Perforant pathway volley (*) and the associated population EPSP recorded in the molecular layer of the dentate gyrus (calibrations, 5 ms and 4 mV). (*Lower Middle*) Differentiated recording of single action potentials associated with the population EPSP when recording in the granule cell layer (calibrations, 2 ms and 40 μV). (*Right*) Undifferentiated recordings from the granule cell layer; overlapped responses to sub- and suprathreshold intensities for population spike activation. Arrows indicate a single action potential evoked by both intensities in an all-or-none fashion (calibrations, 2 ms and 0.4 mV).

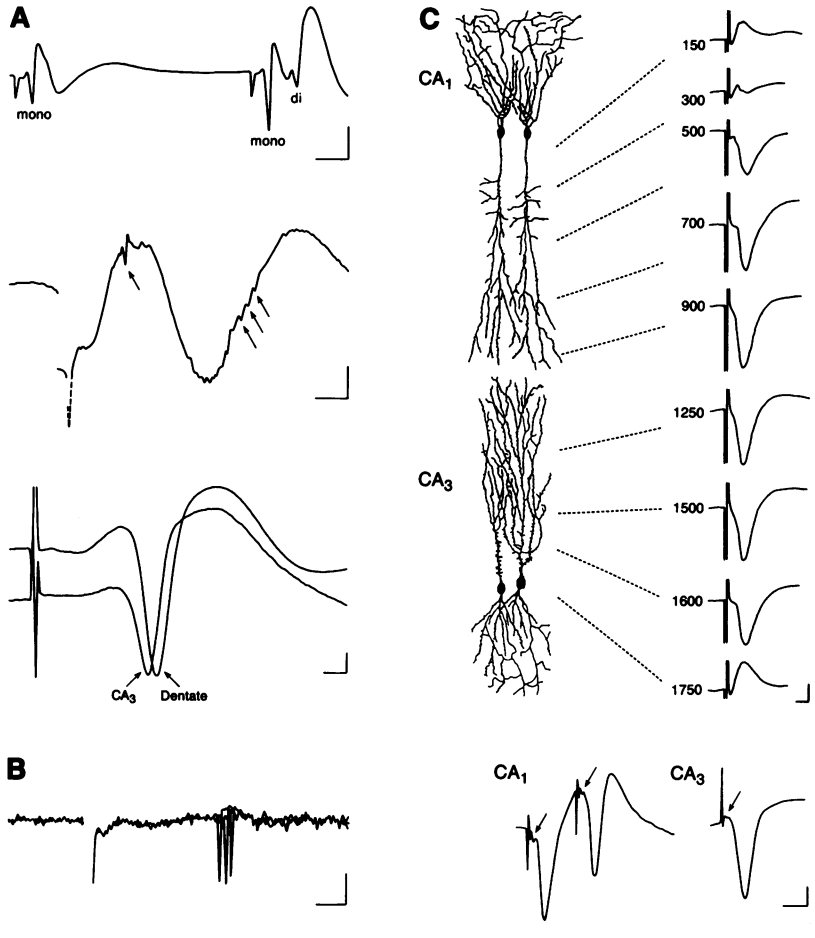

FIG. 2. (*A*) Mono- and disynaptic (di) excitation of CA3 resulting from stimulation of afferents from the entorhinal cortex. (*Top*) Population spikes recorded in the pyramidal cell layer (calibrations, 8 ms and 1 mV). (*Middle*) Single action potentials associated with mono- and disynaptic population EPSPs (calibrations, 2 ms and 0.1 mV). (*Bottom*) Comparison of monosynaptic population spike latencies simultaneously recorded in the pyramidal cell and granule cell layers of CA3 and the dentate gyrus (calibrations: CA3, 1 ms and 0.8 mV; dentate, 1 ms and 0.4 mV). (*B*) Differentiated, single action potentials recorded in the CA1 pyramidal cell layer in response to three consecutive impulses of stimulation to entorhinal cortex fibers (calibrations, 1 ms and 40 μV). (*C*) (*Upper*) Laminar analysis of perforant pathway evoked population EPSPs in CA1 and CA3, demonstrating that maximal synaptic current occurs in the distal dendritic regions. (*Lower*) Evoked perforant pathway fiber volleys (arrows) and population EPSPs recorded in stratum lacunosum-moleculare of CA1 and CA3, respectively (calibrations, 7 ms and 1 mV).

of the hippocampus are reciprocally connected (18), and responses characteristic of antidromic invasion were observed in some preparations. Antidromic responses were clearly distinguishable from monosynaptic orthodromic responses: (*i*) antidromic population and single unit spike latencies (2–3 ms) were shorter and less variable, (*ii*) antidromic population spikes were not preceded by a positive-going wave indicative of synaptic activation, and (*iii*) antidromic responses followed impulses during high-frequency stimulation (200 Hz) of the perforant path with a one-to-one correspondence.

We tested the hypothesis that monosynaptic responses of pyramidal cells represented orthodromic input from excitatory collaterals of adjacent pyramidal neurons activated

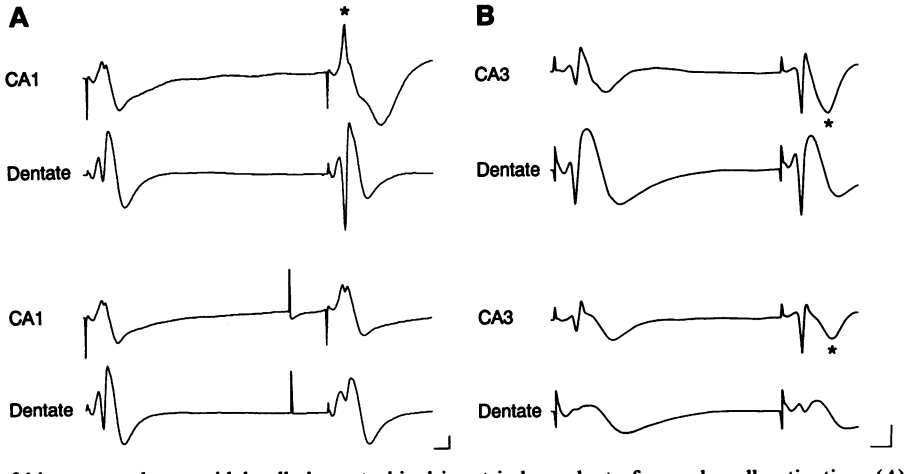

FIG. 3. Excitation of hippocampal pyramidal cells by entorhinal input independent of granule cell activation. (*A*) Selective inhibition of granule cells with stimulation of the contralateral hilus prior to stimulation of afferents from the entorhinal cortex. (*Upper*) Simultaneously recorded responses from the dentate gyrus and CA1 after paired-impulse stimulation to the perforant path. The sharp positivity in the recording from CA1 (*) after the second impulse represents volume conducted source current from the facilitated population spike generated by the discharge of dentate granule cells. (*Lower*) Selective inhibition of the previously facilitated dentate response (and volume conducted signal recorded in CA1) after an intervening impulse to the contralateral hilus (calibrations: CA1, 5 ms and 0.5 mV; dentate, 5 ms and 1 mV); the onset of hilar stimulation is indicated by the positive-going artifact. (*B*) Selective inhibition of dentate granule cells after direct application of muscimol. (*Upper*) Simultaneously recorded responses in the dentate gyrus and CA3 evoked by stimulation of afferents from the entorhinal cortex. (*Lower*) Almost complete inhibition of the dentate population spike after muscimol application with no effect on the monosynaptic response of CA3 pyramidal cells. In contrast, there is a decrease in the late negative wave (*), reflecting a decrease in disynaptic activation via the dentate (CA3 and dentate calibrations, 5 ms and 1 mV).

antidromically (19). For several preparations ($n = 5$) in which both antidromic and orthodromic responses of pyramidal neurons were recorded simultaneously, hippocampal efferents to retrohippocampal regions were transected at a site posterior to the recording electrode and anterior to the stimulating electrode. The tip of a finely tapered surgical blade was inserted into the hippocampus just ventral to the CA1 pyramidal cell layer and moved mediolaterally (from the border of CA1 and subiculum to the border of CA3) so as to transect all fibers carried in the alveus, stratum oriens, and stratum pyramidale. The antidromic population spike was completely eliminated, sparing orthodromic activation through fibers terminating more ventrally. Monosynaptic input to dentate granule cells also was unaffected.

Dissociation of Granule Cell and Pyramidal Cell Responses. Several procedures were used in an attempt to elicit monosynaptic responses of pyramidal neurons in the absence of evoked activity of dentate granule cells. In one set of experiments, inhibitory input from the contralateral dentate was used to suppress the granule cell response to excitatory entorhinal input (20). Paired-impulse stimulation of entorhinal cortical axons, with a single intervening impulse delivered to the hilus of the contralateral dentate, preferentially suppressed facilitation of granule cell excitation without affecting monosynaptic excitation of pyramidal cells (Fig. 3*A*). Similarly, local pressure ejection of the γ-aminobutyric acid type A agonist muscimol into the dentate gyrus increased suppression of granule cells, particularly in response to short interstimulus intervals, with no change in the simultaneously recorded short-latency response of CA3c neurons (Fig. 3*B*).

Relative Strengths and Frequency Dependence of the Monosynaptic and Trisynaptic Inputs. In a final series of experiments, the relative strengths of mono- and trisynaptic inputs originating from one set of entorhinal cortical axons (one stimulation site) to CA1 pyramidal neurons were compared. Results showed that suprathreshold, long-latency responses of CA1 pyramidal cells attributable to trisynaptic pathway excitation were seen only rarely when using low-frequency stimulation (0.2 Hz). In contrast, suprathreshold monosynaptic responses almost always were observed. Monosynaptic discharges commonly were followed by two waves of subthreshold excitation (population EPSPs only) with latencies corresponding, respectively, to disynaptic input from entorhinal excitation of CA3 (9–13 ms) and trisynaptic input from entorhinal excitation of the dentate gyrus (16–21 ms; Fig. 4*A*). Propagation of perforant path input through the trisynaptic pathway to CA1 reached suprathreshold levels only with higher stimulation frequencies of 5–15 Hz. Analogous observations were made with respect to mono- and disynaptic input to CA3 pyramidal cells. Recording sites were varied along the longitudinal axis of the hippocampus (i.e., perpendicular to the orientation of the trisynaptic pathway) for a distance of 5 mm, as well as transverse to the longitudinal axis (i.e., parallel to the orientation of the trisynaptic pathway) from CA3 to the CA1/subicular border. The predominance of low-frequency monosynaptic excitation and a 5- to 15-Hz frequency facilitation of trisynaptic excitation were characteristic of pyramidal neurons sampled at all locations.

DISCUSSION

The results of these experiments demonstrate that excitation of hippocampal pyramidal neurons by input from the entorhinal cortex does not occur primarily because of sequential propagation through the trisynaptic pathway. Instead, an afferent volley from the entorhinal cortex induces nearly simultaneous monosynaptic excitation of all three major subfields of the hippocampus. Evoked responses of CA3 pyramidal cells often preceded evoked responses of dentate granule cells, and responses of CA1 pyramidal cells were coincident or nearly coincident with those of dentate granule cells. Disynaptic activation of CA3 and both di- and trisynaptic activation of CA1 also were observed. The latency of the disynaptic response in CA1 was consistent with monosynaptic excitation of CA3 and the subsequent excitation of CA1 through transmission via Schaffer collaterals. These polysynaptic responses generally were subthreshold for spike generation. Suprathreshold polysynaptic excitation was obtained primarily with trains of stimulation that induced frequency facilitation of granule cell responses. Finally, activity in CA3 and CA1 could be evoked when dentate granule cell activity was either blocked or greatly inhibited, indicating that entorhinal-induced excitation of pyramidal neurons can occur independently of granule cell excitation.

Although the hippocampus has been the focus of an extraordinary number of electrophysiological investigations in the past 3 decades, surprisingly few studies have focused specifically on the entorhinal projection to Ammon's horn. As noted above, the use of an *in vitro* slice preparation cannot evaluate the relative potencies of mono- and trisynaptic inputs that arise from the same subpopulation of entorhinal neurons. Although incidental observations of short-latency discharges of single hippocampal units evoked upon stimulation of the entorhinal cortex have been reported (9, 10), short-latency field potentials recorded in Ammon's horn

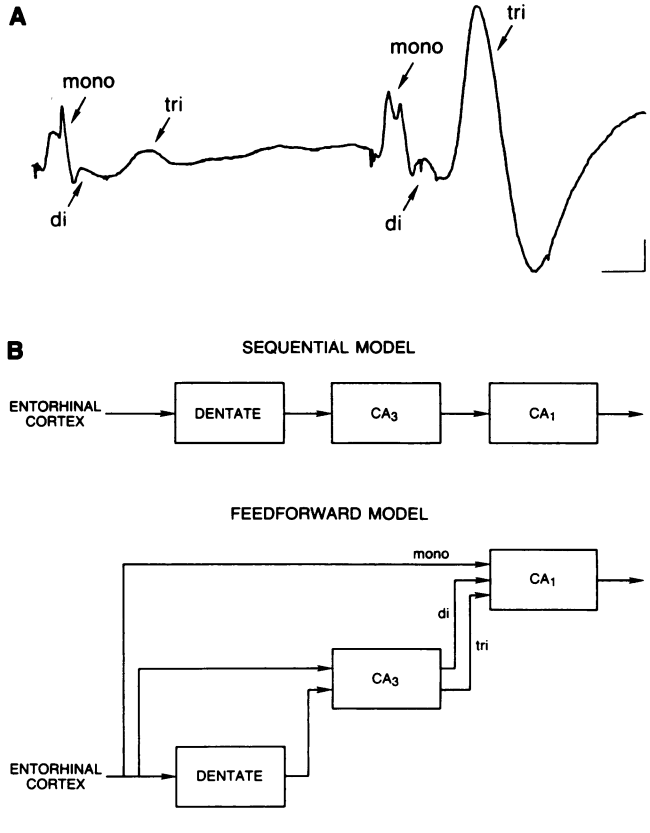

FIG. 4. (*A*) Demonstration of feedforward excitation of CA1 by paired impulse stimulation of afferents from the entorhinal cortex. Arrows indicate the monosynaptically activated population spike (mono: first negative-going component; see Fig. 3 regarding contamination by field-propagated response from dentate), followed by a disynaptically evoked single action potential with associated population EPSP (di), and the trisynaptic (tri) population EPSP (calibrations, 10 ms and 1 mV). (*B*) (*Upper*) Schematic representation of the traditional model of sequential propagation of activity through the trisynaptic pathway. (*Lower*) Schematic representation of the proposed model of a two-phase feedforward excitation of CA1 pyramidal neurons.

often have been attributed to volume conduction from granule cell discharge in the dentate gyrus (5, 16, 21, 22). Explicit tests of the volume conduction hypothesis have not been performed, however, and the data reported here rule out such a possibility: (*i*) evoked responses of dentate granule cells that are volume conducted to CA1 are opposite in polarity to the monosynaptic responses of CA1 pyramids (see Fig. 3); (*ii*) evoked field potential responses in CA3 can be shorter in latency than those evoked in the dentate; (*iii*) single unit discharges evoked in both CA1 and CA3 occur with probabilities and latencies consistent with the amplitudes and latencies, respectively, of short-latency population spikes recorded in those same regions; (*iv*) short-latency population spikes recorded in the CA3 region initially decline in amplitude as recording electrodes are moved closer to the dentate (data not shown); and (*v*) short-latency population spikes recorded in CA3 can occur in the near absence of population spikes in the dentate gyrus.

The predominance of monosynaptic excitatory input may explain a number of seemingly contradictory observations documented in past investigations of the behavioral correlates of dentate granule and hippocampal pyramidal neurons. For example, classical conditioning studies have found that conditioned stimuli (CS) controlling animals' behavior can elicit responses from CA3 pyramidal neurons, which have a shorter latency than responses recorded from any other subfield of the hippocampus (23). Moreover, hippocampal pyramidal neurons can exhibit CS-evoked patterns of activity that are qualitatively different than those of dentate granule cells (24–26) and yet similar to the CS-evoked activity of entorhinal cortical neurons recorded within the superficial layers projecting to the hippocampus (27). Likewise, unit activity of both hippocampal and entorhinal neurons correlates with spatial location during food retrieval within a maze (28, 29). In contrast, dentate granule cells display a phasic bursting pattern of spike discharge (correlated with θ rhythm; refs. 26 and 30), which is at best weakly correlated with spatial location (31). In addition, destruction of dentate granule cells does not result in the abolition of spatial field correlates of hippocampal pyramidal neurons (32). The findings reported here provide a basis for reconciling these apparent discrepancies: excitatory input from the entorhinal cortex can be a stronger determinant of pyramidal cell output than excitatory input from the dentate gyrus.

In total, these results argue for a new conceptualization of the functional organization of the hippocampal formation with respect to the propagation of activity through its intrinsic pathways (Fig. 4*B*). Excitatory input from the entorhinal cortex initiates a two-phase feedforward excitation of pyramidal cells, with the dentate gyrus providing feedforward excitation of CA3 and with both the dentate and CA3 providing feedforward excitation of CA1.

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