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COMMENTARY

TWO-STAGE MODEL OF MEMORY TRACE FORMATION: A ROLE FOR "NOISY" BRAIN STATES*

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Abstract—Review of the normally occurring neuronal patterns of the hippocampus suggests that the two principal cell types of the hippocampus, the pyramidal neurons and granule cells, are maximally active during different behaviors. Granule cells reach their highest discharge rates during theta-concurrent exploratory activities, while population synchrony of pyramidal cells is maximum during immobility, consummatory behaviors, and slow wave sleep associated with field sharp waves. Sharp waves reflect the summed postsynaptic depolarization of large numbers of pyramidal cells in the CA1 and subiculum as a consequence of synchronous discharge of bursting CA3 pyramidal neurons. The trigger for the population burst in the CA3 region is the temporary release from subcortical tonic inhibition.

An overview of the experimentally explored criteria of synaptic enhancement (intensity, frequency, and pattern of postsynaptic depolarization, calcium influx, cooperativity, threshold) suggests that these requirements may be present during sharp wave-concurrent population bursts of pyramidal cells. Experimental evidence is cited showing that (a) population bursts in CA3 may lead to long-term potentiation in their postsynaptic CA1 targets, (b) tetanizing stimuli are capable of increasing the synchrony of the sharp wave-burst, and (c) activity patterns of the neocortical input to the hippocampus determine which subgroup of CA3 neurons will trigger subsequently occurring population bursts (initiator cells).

Based on the experimental evidence reviewed a formal model of memory trace formation is outlined. During exploratory (theta) behaviors the neocortical information is transmitted to the hippocampus via the fast-firing granule cells which may induce a weak and transient heterosynaptic potentiation in a subgroup of CA3 pyramidal cells. The weakly potentiated CA3 neurons will then initiate population bursts upon the termination of exploratory activity (sharp wave state). It is assumed that recurrent excitation during the population burst is strongest on those cells which initiated the population event. It is suggested that the strong excitatory drive brought about by the sharp wave-concurrent population bursts during consummatory behaviors, immobility, and slow wave sleep may be sufficient for the induction of long-term synaptic modification in the initiator neurons of the CA3 region and in their targets in CA1. In this two-stage model both exploratory (theta) and sharp wave states of the hippocampus are essential and any interference that might modify the structure of the population bursts (e.g. epileptic spikes) is detrimental to memory trace formation.

CONTENTS

*Dr Buzsáki wishes to dedicate this paper to his mentor and friend, the late Endre Grastyàn.

Abbreviations: CA, cornu Ammonis; EEG, electroencephalogram; EPSP, excitatory postsynaptic potential; IPSP, inhibitory postsynaptic potential; LTP, long-term potentiation; NMDA, *N*-methyl-D-aspartate; RSA, rhythmic slow activity; SPW, sharp wave.

1. INTRODUCTION

The idea that modification of synaptic function can provide a basis for memory arose shortly after the discovery of the synapse.[10,119,129] Since the early days various models have been proposed in which information is represented by combinations of the firing patterns of individual neurons. In many of these models, memory is due to activity-dependent changes in neuronal connections and the resulting change preferentially enhances subsequent occurrences of that activity pattern during recall.[52,71,83,94] An impetus for research in this direction came with the demonstration of long-lasting synaptic modification after high-frequency activation, termed long-term potentiation (LTP).[17,144]

Following Hebb,[71] several models offered potential explanations of how LTP might occur in the normal brain.[11,86,94,98] Most of these models are based on existing knowledge of anatomical circuitries, but they tend to ignore physiological states in which connections within these circuitries are active or suppressed. An approach, common to most models, is to compare the brain with man-made machines (e.g. computers) and to offer algorithms for computations in brain circuitries based on solutions in the models.[96] A theoretical problem with this approach is that the core of brain function is not the exertion of logical or control operations upon the outside world but its representation by an internal model.[42,53,115] A practical problem of the computer analogy is the assumption that information is "printed" into an ever-ready, silent, tabula rasa-type neuronal network. If variability enters at all into such models, it is considered in terms of noise in a signal which is taken to be the main manifestation of variation.[153,155] At first glance the silent-network approach seems to gain support from the biological data base demonstrating more efficient information processing when neuronal activity is largely suppressed.[9,111,130] However, if we accept the view that the brain must be "aroused"[109] in order to function, then we are faced with the question of what the brain does during half of its computing time. If the "non-aroused", synchronous state of the neuronal populations is merely a "stand-by" mode then we must address the evolutionarily relevant point why the nervous system is not hard-wired exclusively for the information processing mode, similar to the computers. As will be pointed out, synchronous population bursts are a very risky invention because their malfunctioning readily leads to epileptic activity.

The main objectives of this review are (a) to examine physiologically occurring neuronal patterns that might meet the experimentally explored criteria of LTP; (b) to consider that the memory trace may be formed during "non-aroused" states of the brain; and (c) to propose possible rules which may allow "noisy" neuronal activity to carry highly specific information.

2. BEHAVIOR-DEPENDENT ELECTRICAL FIELD (ELECTROENCEPHALOGRAM) AND CELLULAR ACTIVITY IN THE HIPPOCAMPUS

Hippocampal rhythmic slow activity (RSA or theta) has been implicated in several functions, ranging from sensory processing to the voluntary control of movement.[16,67,150,152] In the rat, hippocampal theta activity occurs during exploratory behaviors, such as sniffing, rearing, walking and the paradoxical phase of sleep.[150] In the absence of theta, irregular sharp waves (SPWs) of 40–120 ms duration occur in the hippocampal record (Fig. 1). SPWs are observed, in the order of frequency, during slow wave sleep, awake immobility, drinking, eating, face washing, and grooming.[26,34,110,138] The incidence of SPWs ranges from 0.02 to 3/s during awake immobility. Both theta waves and SPWs occur essentially synchronously in both hippocampi and along the longitudinal axis of the structure (Figs 1–4).

Cellular correlates of theta and SPW are characteristically different. Granule cells of the dentate gyrus fire rhythmically during theta waves and show a five- to eight-fold increase in discharge frequency (up to 80/s) relative to non-theta states.[34,46,122] On the other hand, pyramidal cells of the CA fields, on average, show a decreased discharge frequency during theta electroencephalogram (EEG).[34,110,112,120,137] Although some "spatially sensitive"[110] neurons may show sustained firing at 4–8/s when the rat walks through the "spatial field" of the cell, most pyramidal cells fire at

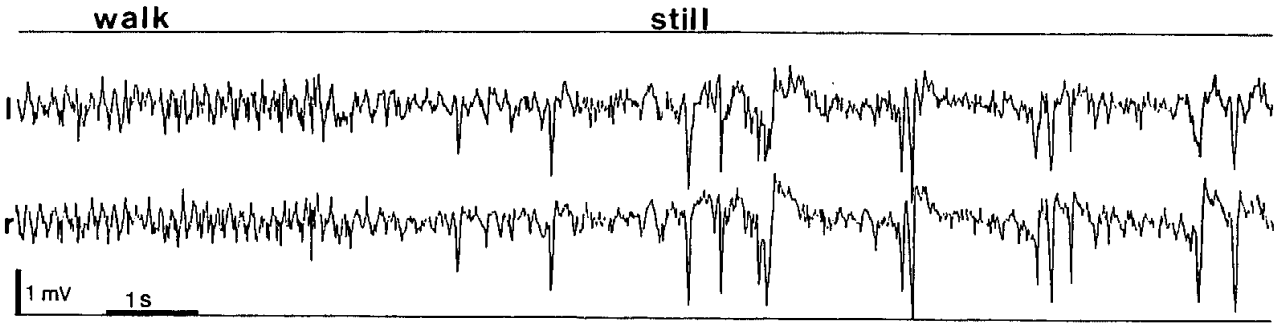

Fig. 1. EEG recorded from the stratum radiatum of the left (l) and right (r) CA1 region of the hippocampus during walk–immobility (still) transition. Note regular theta waves during walking and large monophasic SPWs during immobility. Note also the bilaterally synchronous nature of SPWs.

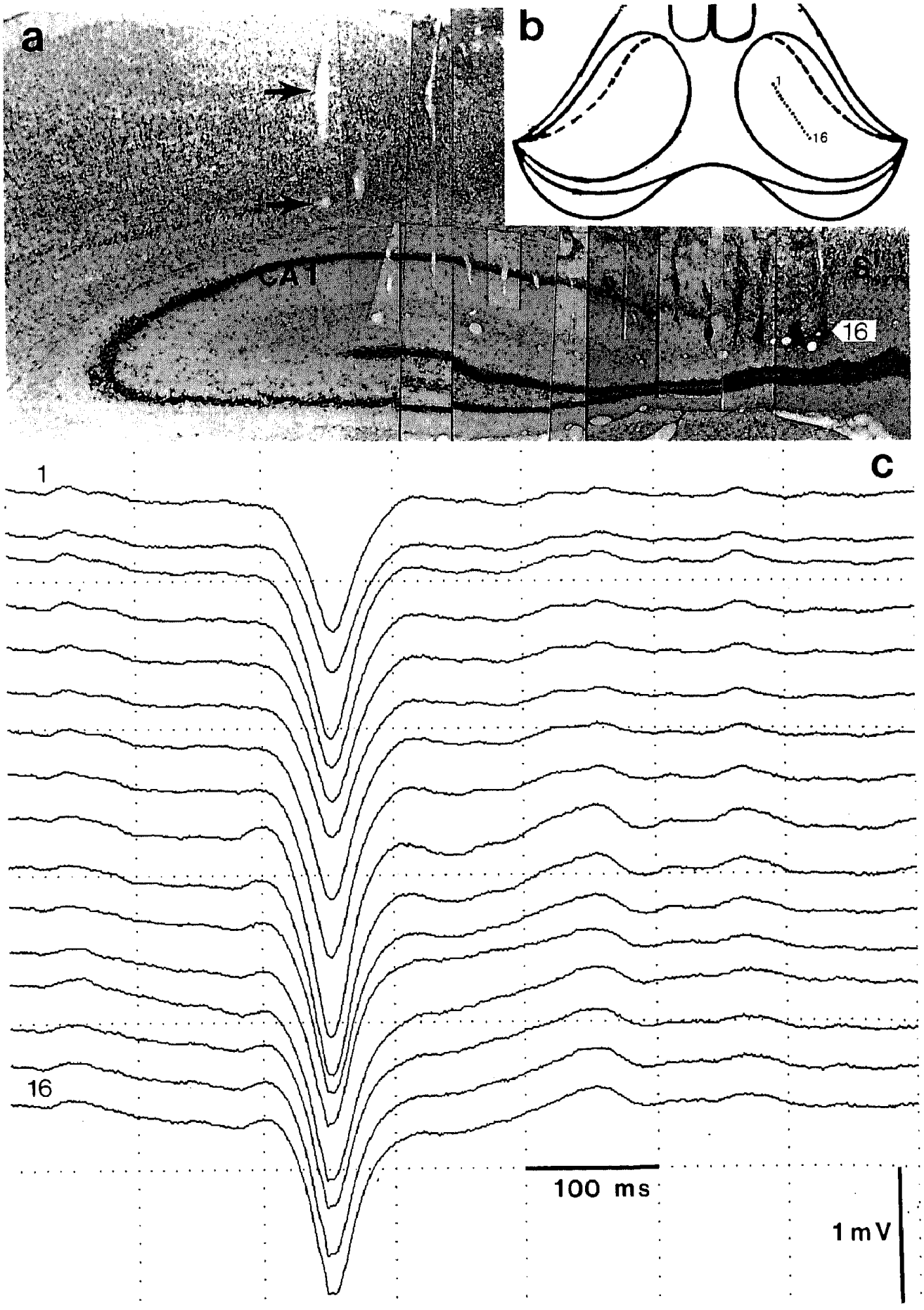

Fig. 2. Averaged SPW ($n = 50$) recorded simultaneously from 16 microelectrodes along the longitudinal axis of the CA1 region of the hippocampus (a and b). (a) Photomontage of the electrode tracks. (b) Dorsal view of the hippocampal formation. Dots 1–16 indicate the positions of the microelectrodes. Spacing between electrodes is 200 μm. All tips were positioned in the stratum radiatum. Note simultaneous occurrence of SPWs over a distance of 3.2 mm (c).

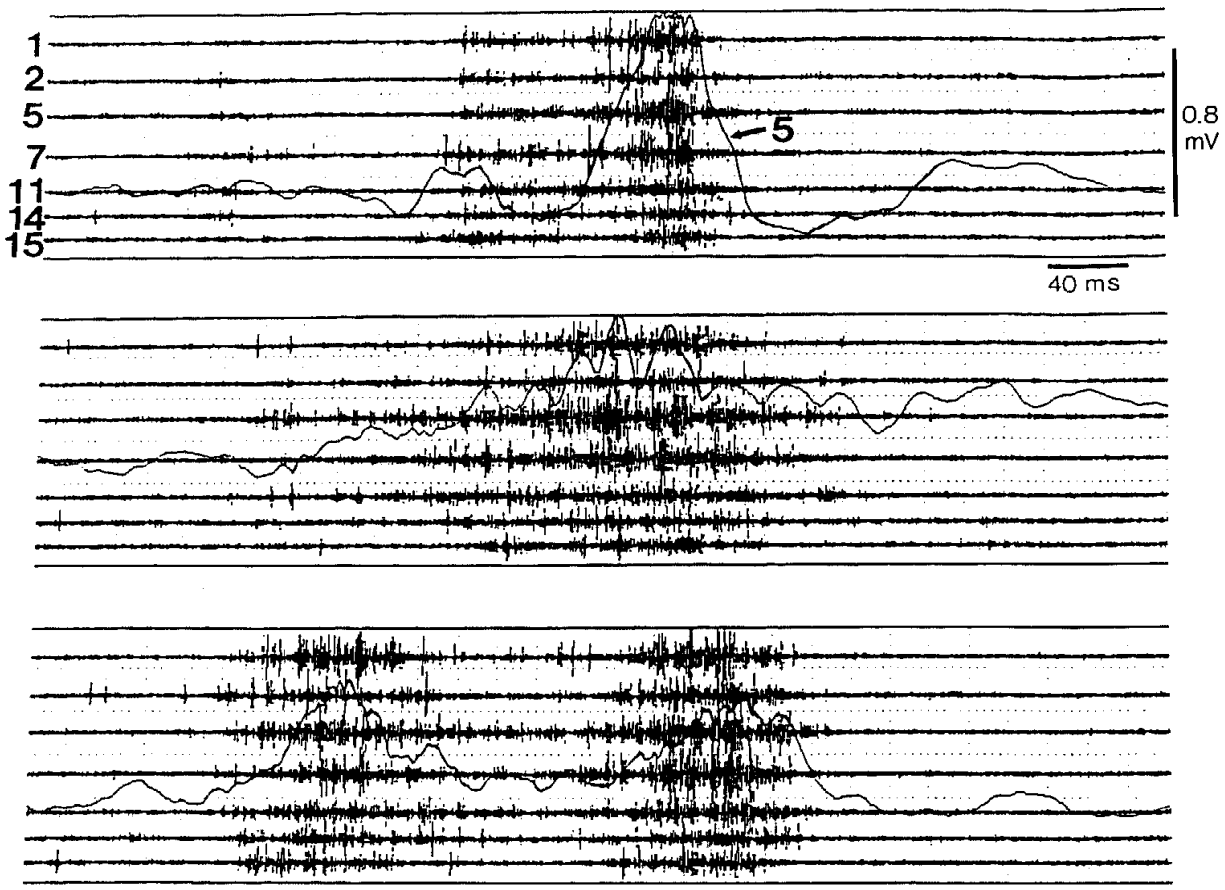

Fig. 3. SPW-concurrent population bursts recorded during awake immobility along the longitudinal axis of CA1 pyramidal layer. Sixteen-electrode probe.[38] The figures to the left of the traces designate the sequence of the microelectrodes (see Fig. 2b). Spacing between successive electrodes is 200 μm. Only seven derivations with acceptable unit activity are shown. The filtered trace (1–70 Hz) was derived from electrode 5 (arrow). Note the synchronous nature of population bursts at all electrodes. The three panels indicate variations of SPW-bursts (narrow, wide and doublet).

0.01–0.5/s, or stop discharging altogether during theta-related behaviors.

The firing pattern of pyramidal cells changes substantially at the cessation of exploratory behavior. Importantly, groups of pyramidal cells in CA1–CA3 and subiculum now fire in synchronous bursts associated with the field SPW (Figs 3 and 4). Interneurons also display a significant frequency increase during the SPW-burst[34,110] and there is very little neuronal activity of any kind in between successive SPWs. Granule cells may also fire in concert with the SPW, but their frequency remains below that observed during theta-associated behaviors.[26]

An important thesis of this paper is that behaviors associated with the highest neuronal firing rates and most synchronous population discharges (co-activation) create the most favorable conditions for the enhancement of synaptic plasticity. We tentatively suggest that plastic changes in the pyramidal cells of the hippocampus may take place during SPW-associated population bursts. In this context it is important to note that SPWs are present also in the primate hippocampus, including that of humans, but rhythmic extracellular currents, comparable to the rodent or feline hippocampal theta, have not yet been reported in primates.[7,45,58,59]

2.1. *Sequential activation of the unidirectional hippocampal circuitry*

The perforant path which originates in the entorhinal cortex and terminates on the dendrites of the granule cells and distal apical dendrites of the pyramidal cells constitutes the principal afferent path to the hippocampal formation.[75,136] There are approximately one million granule cells in the dentate gyrus of the rat.[19,127] There is a substantial convergence of entorhinal cells on the dendrites of individual granule cells and the perforant path is estimated to contact about 4000 spines on each granule cell.[49,93]

The dentate granule cells give rise to the mossy fibers, which terminate on both neurons in the polymorphic zone of the dentate hilus[4] and the proximal dendrites of the CA3 pyramidal cells. There are about five times fewer pyramidal cells in the CA3 region than there are granule cells in the dentate gyrus.[20] Because each mossy fiber terminates on about 10–15 pyramidal cells,[43] each CA3 pyramidal cell is therefore innervated by approximately 50–100 granule cells.

Pyramidal cells of CA3 give rise to very extensive subcortical and intrahippocampal projections. The associational connections of the CA3 pyramidal

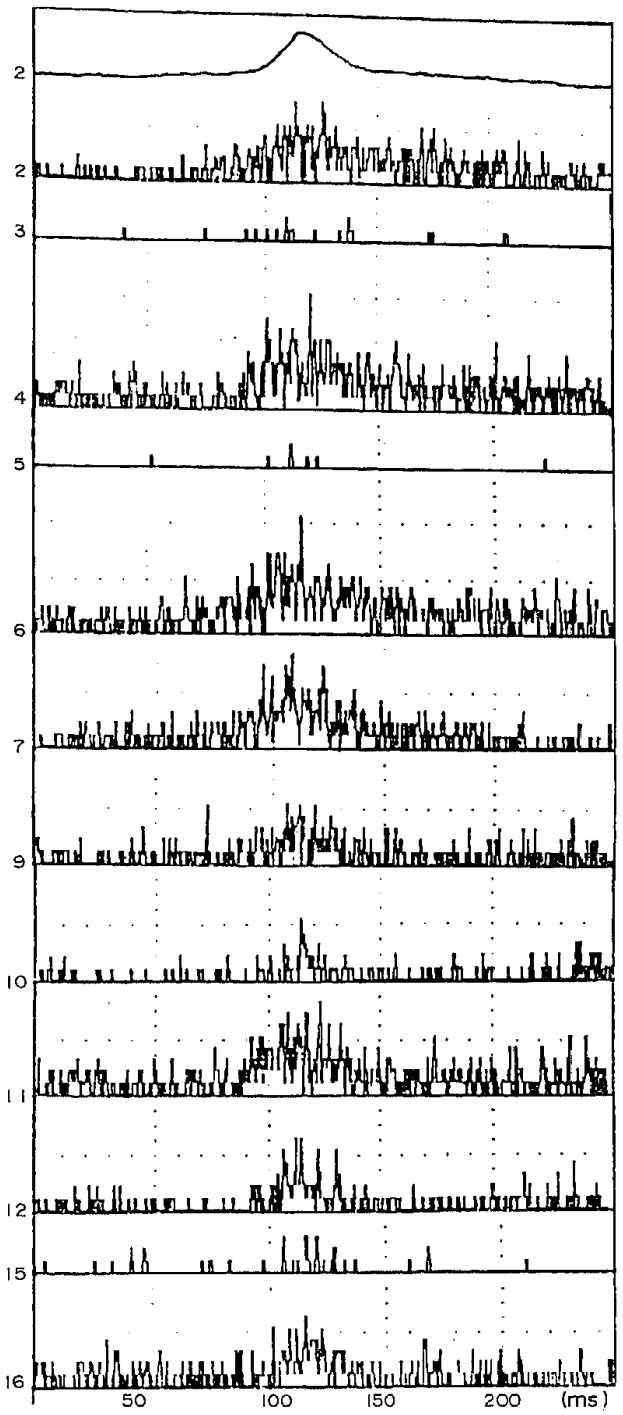

Fig. 4. SPW-triggered histograms of cellular activity recorded along the longitudinal axis of the CA3 pyramidal layer. Sixteen-electrode probe.[38] The figures to the left of the histograms designate the sequence of the microelectrodes (see Fig. 2b). The filtered trace (electrode 2; 1–70 Hz) and the histograms are averages of 50 repetitions. Traces 3 and 5 were constructed from isolated single pyramidal neurons while all other histograms reflect multiple unit activity such as shown in Fig. 3. Note tight synchrony of population activity of CA3 pyramidal cells during SPW.

neurons cover virtually the whole extent of the rostrocaudal extent of the entire CA3 region.[79,143] Despite this widespread population divergence, any particular CA3 cells is probably innervated by less than 5% of the total CA3 neurons.[133]

CA3 pyramidal cells also send axons, termed Schaffer collaterals,[89,124,141] to the pyramidal cells of the CA1 region. There are slightly more neurons in the CA1 region of the rat (about 250,000) than in the CA3 region.[126] CA3 pyramidal cells located closest to the dentate gyrus (CA3c) project mainly to apical dendrites of the subicular portion of the CA1 region, and neurons near the CA3/CA2 border (CA3a) send their axons mainly to the basal dendrites of the nearby CA1 cells.[79,143]

CA1 axons project dominantly to the subiculum, but some fibers reach the entorhinal cortex.[13,55,142] The subiculum is the major output region of the hippocampal formation,[85,149] and its afferents to the deep layers of the entorhinal cortex complete the unidirectional multisynaptic entorhinal cortex–hippocampus–entorhinal cortex chain.

The extensive divergent–convergent pathways pose the question of how the fidelity of neuronal information is preserved in this system.[94,133] For the various computational models of the hippocampus it is essential to know whether the neuronal pattern sent out from hippocampal circuitry could be returned to the same entorhinal neuronal population that originated it. Our recent physiological findings suggest that this indeed may be the case.

The efficacy of spread of neuronal activity in a multisynaptic system can be tested by delivering test volleys and observing the magnitude of the electrical responses throughout successive neuronal populations. When the perforant path is stimulated, evoked neuronal activity can be monitored at each subregion of the hippocampal formation.[5,14] In the freely moving rat the amplitude of the evoked responses varies with the behavior of the animal.[156] Both monosynaptic, and especially multisynaptic, responses are attenuated during theta-related exploratory states and are relatively large during consummatory behaviors.[33,92,156] The trisynaptically evoked CA1 response is virtually missing during exploratory behaviors (Fig. 5).[26,34] The suppression of intrahippocampal spread of neuronal impulses is probably controlled by subcortical afferents because stimuli delivered during SPWs evoked potentials two to four times larger as compared to responses evoked in between SPWs,[26] and because removal of the subcortical inputs by fimbria–fornix lesion results in a large increase of the excitability of the hippocampal cells.[32,40]

When stimuli are delivered to the perforant path during an SPW-burst or when stimulation is done in animals with fimbria–fornix lesion,[30] single volleys occasionally evoke double or triple responses (Fig. 6). These multiple responses are due to the reverberation of neuronal impulses in the hippocampus–entorhinal cortex–hippocampus circuitry. A complete cycle requires about 20–25 ms. While recording from isolated single cells we frequently observed that if a neuron responded to the first cycle, its response to the second cycle was very likely (Fig. 6a). This observation raised the intriguing possibility that despite the considerable anatomical divergence of the intrahippocampal

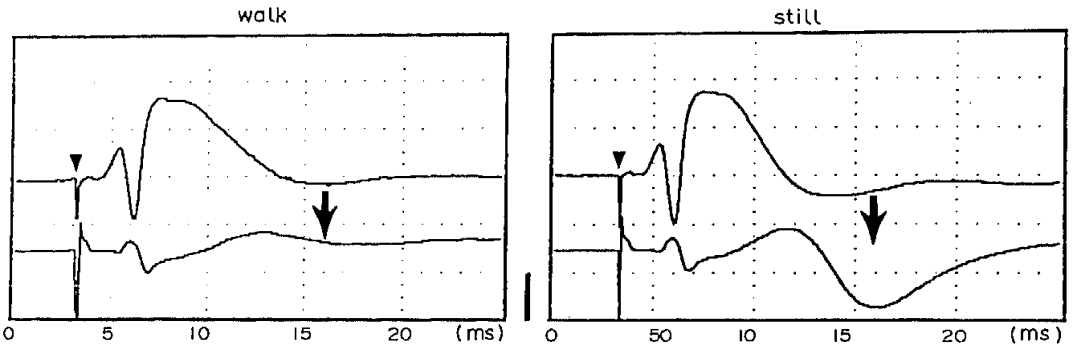

Fig. 5. Simultaneously recorded evoked potentials in the hilus of the dentate gyrus (upper traces) and the stratum radiatum of CA1 (lower traces) in response to perforant path stimulation (arrowhead). Note large-amplitude response (Schaffer potential; arrow) in CA1 during immobility (still) and its absence during walking, despite similar potentials in the dentate gyrus. Single responses. Calibration: 5 mV.

projections, cellular groups do not mix the neuronal information at the successive stages of the hippocampal circuitry but are able to return the "afferent copy" to the cells of origin in the entorhinal cortex.[34]

To test this possibility, we inserted 16 microelectrodes along the longitudinal axis of the CA1 region of the dorsal hippocampus[38] and monitored the evoked potentials in response to perforant path stimulation. The perforant path was stimulated with single pulses of low intensity to avoid the suppressive effects of recurrent inhibition on reactivation of cellular groups. Occasionally, the single volleys evoked double responses. Importantly enough, the spatial distribution of the amplitude of the responses

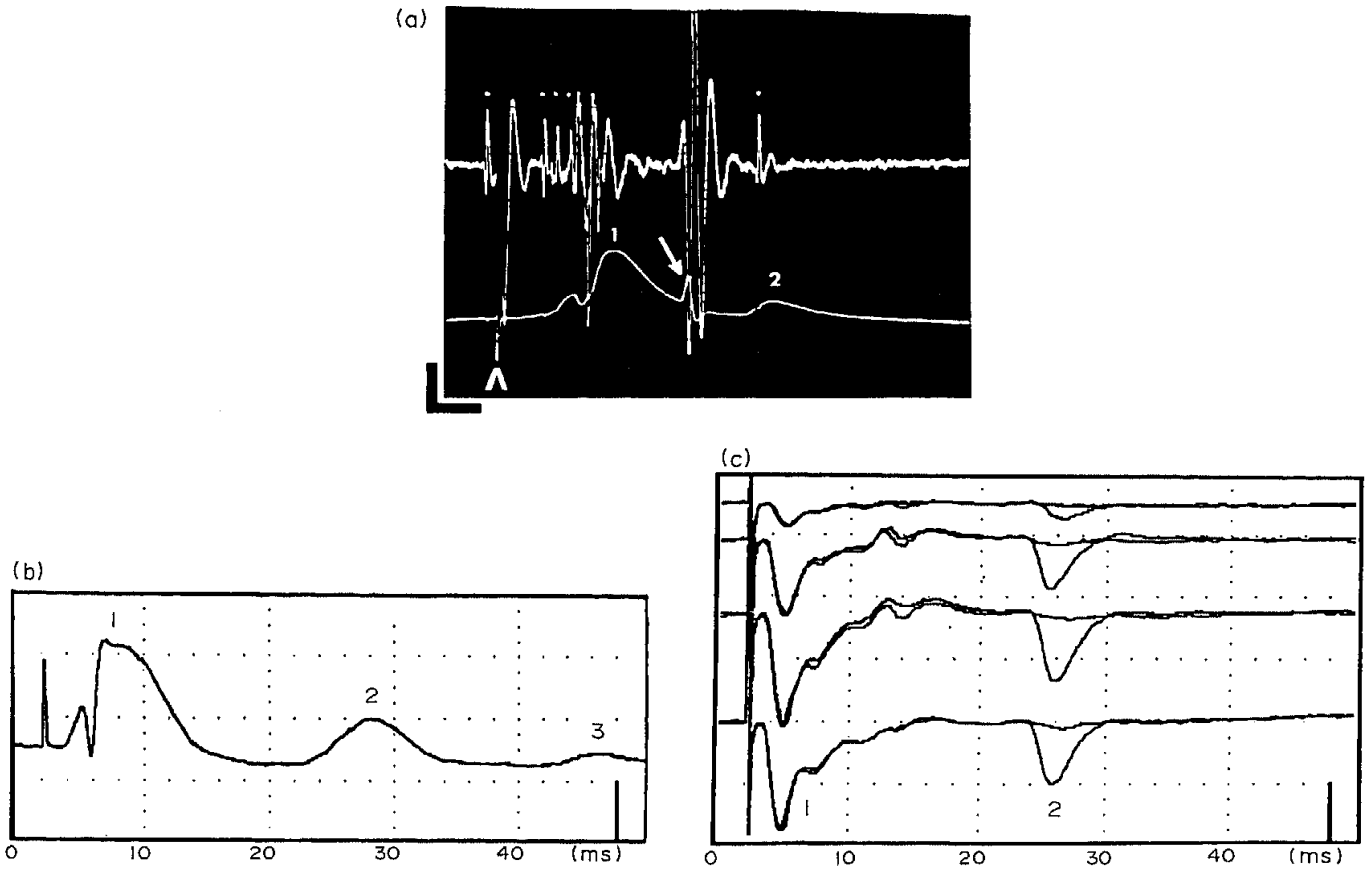

Fig. 6. Reverberation on neuronal activity in the hippocampus–entorhinal cortex circuitry. (a) Isolated interneuron[29] and field potential recorded in the CA1 pyramidal layer with the same microelectrode in response to single pulse stimulation of the commissural input (white arrowhead). White dots: action potentials. White arrow: volume-conducted population spike from the dentate gyrus. 1 and 2: direct and multisynaptically evoked responses, respectively. Calibrations: 5 ms; 2 mV. (b) Triple responses in the granule cell layer of the dentate gyrus to single pulse stimulation of the perforant path. (c) Double responses (1 and 2) in the molecular layer of the dentate gyrus to perforant path stimulation. Two superimposed consecutive responses. Note identical early responses (1) and the all-or-none nature of the reverberating (2) response. The four traces wre simultaneously recorded with microelectrodes inserted 400 μm from each other along the longitudinal axis of the dentate gyrus (see Fig. 2b). Calibrations: 5 mV (b); 2 mV (c). (a) and (b) intact animals; (c) rat with fimbria–fornix lesion.[32,40]

in the two cycles was virtually identical (Fig. 7). Apparently, this was possible only if the second response was evoked by the same or closely overlapping Schaffer collaterals.

The unexpectedly high fidelity of the returned afferent copy may be explained by several hypothetical mechanisms. First, the entorhinal–hippocampal–entorhinal circuitry may be hard-wired,[5] similar to the sensory systems. The anatomical observations, summarized above, do not lend support to such point to point connections. Second, the first response may have created a highly excitable "focus" with surrounding inhibition in the CA3 region, and these same cells could have been reactivated predominantly because of their lowered threshold, even though mossy fibers might have excited a larger portion of the CA3 region in a relatively diffuse manner. This possibility is supported by our observation that double responses were also present in CA1 when the second dentate response was very small or not notable in the field recording.[34] The third possibility is that stimulation of the perforant path fibers backfired a circumscribed subpopulation of layer II neurons in the entorhinal cortex and the returning excitation from the hippocampus might have preferentially activated this neuronal group because of its relative hyperexcitability. Simultaneous recordings of neuronal patterns at each of the relay regions of the entorhinal cortex–hippocampus axis might offer some insights about the mechanisms of impulse transfer from one subregion to the next.

In summary, our physiological findings lend sup-

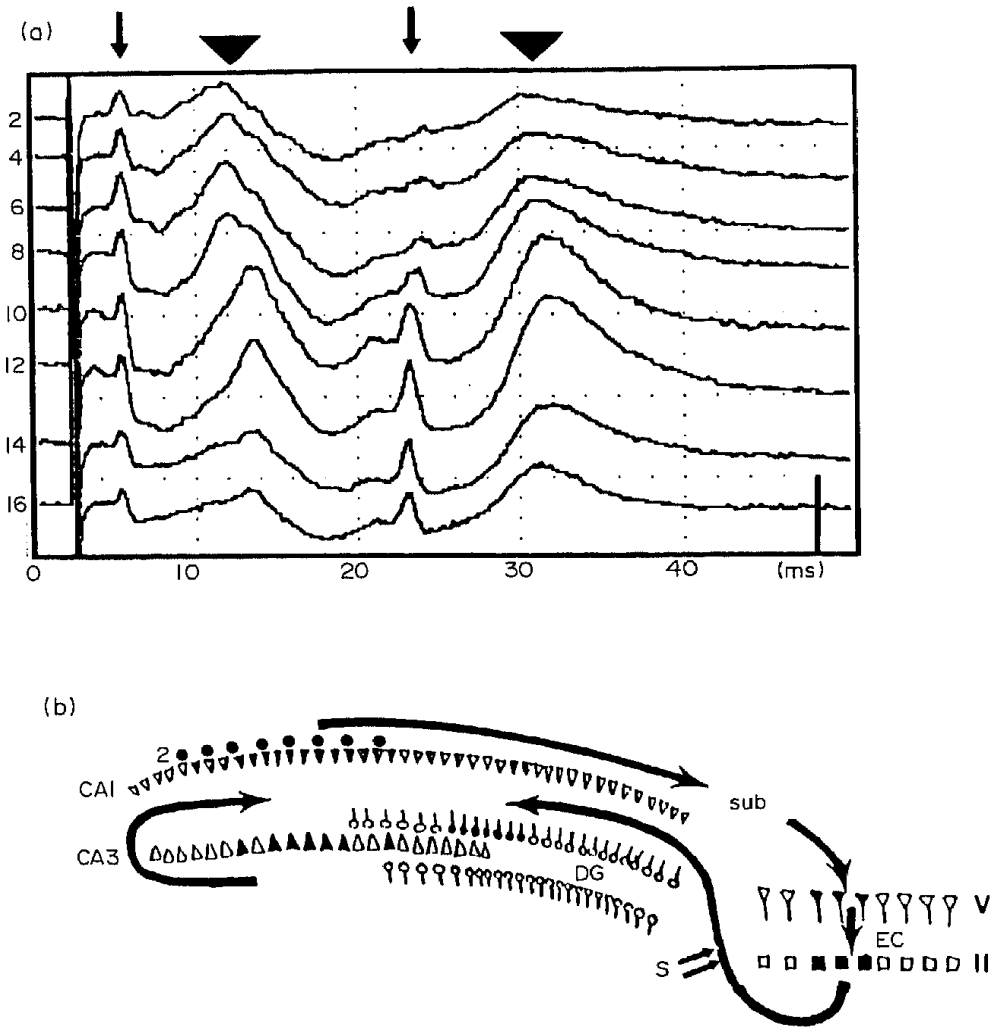

Fig. 7. Reverberation of neuronal impulses in the entorhinal cortex–hippocampus–entorhinal circuitry. (a) Simultaneously recorded field potentials from the stratum oriens of CA1 in response to single pulse stimulation of the perforant path. The distance between recording sites was 400 μm along the longitudinal axis of the hippocampus (see Fig. 2b). Arrows: volume-conducted population spikes from the dentate gyrus. Large arrowheads: field responses generated in CA1. Note virtually identical spatial distribution of the early and late responses. Fimbria–fornix lesioned rat.[40] (b) Circuit diagram of the neuronal events in a. Electrical stimulation (s) of the perforant path evoked neuronal firing of the granule cells of the dentate gyrus (DG), the CA3 and CA1 regions (filled cells). Dots in CA1 indicate the positions of the recording electrodes 2–16. The population discharge of CA1 pyramidal neurons sequentially activated neurons in the subiculum (sub) and layer V of the entorhinal cortex (EC) which, in turn, reactivated the same population of layer II stellate cells (filled squares) whose axons were previously stimulated by the electrical pulse. These stellate neurons, in turn, reactivated the same or closely overlapping neuronal populations in the trisynaptic circuitry as during the first cycle.

port to the suggestion that previously active neurons in the entorhinal cortex may be selectively reactivated by the hippocampal output under certain conditions.

2.2. *Control of sharp waves*

Depth profile analysis has revealed that the amplitude maxima of SPW (largest negativity in stratum radiatum of CA1; <2.5 mV) correspond to the terminals of the intrahippocampal associational pathways.[26] The trigger for an SPW is a synchronous population burst of CA3 pyramidal cells and hilar neurons.[26,34,139] The bilaterally simultaneous bursts along the whole longitudinal extent of the CA3 and hilar regions may be explained by assuming that population bursts are triggered by a relatively few cells in the CA3 axis and recruitment of more cells occurs in "patches" around the burst initiator neurons when the hippocampus is temporarily released from subcortical inhibition (see below). Population synchrony is further facilitated by the extensive recurrent axon collaterals of CA3 and CA2 neurons.[79,143]

SPWs in CA1 are assumed to represent synchronous excitation (excitatory postsynaptic potential, EPSP) of pyramidal cells by the Schaffer collaterals of CA3 neurons coupled with somatic inhibitory postsynaptic potentials (IPSPs) produced by interneurons. It is suggested that dendritic excitation is capable of overriding somatic and feed-forward dendritic inhibition,[29] resulting in a secondary population burst of CA1 pyramidal cells. SPWs in the inner molecular layer of the dendate gyrus are explained similarly, but the trigger zone is the hilar region.[26]

While theta activity requires an extra-hippocampal "pacemaker" command,[116] SPWs are assumed to be intrinsic to the hippocampus, i.e. they are not induced actively by an extra-hippocampal input. Indeed, subcortical afferents may exert a tonic suppressive action on the synchronizing mechanism of the CA3 and hilar regions. When the subcortical inputs (both cholinergic and noncholinergic[34]) are temporarily reduced the cessation of suppressive action releases the triggering CA3 and hilus neurons giving rise to bilaterally synchronous SPWs. Implicit in this suggestion is the prediction that removal of the subcortical inputs would release population bursts in the hippocampus. Indeed, surgical transection of the subcortical afferents (fimbria–fornix lesion) results in large-amplitude SPWs and EEG spikes.[39,40] Furthermore, the predominant activity of the relatively isolated hippocampal transplant is highly synchronous population bursts.[36]

3. SHARP WAVES AS A PHYSIOLOGICAL CANDIDATE OF LONG-TERM POTENTIATION

Whatever physiological electric patterns may eventually prove to be the substrate of long-term potentiation (LTP), they should meet the basic requirements for the elicitation of LTP, such as the necessity of strong synaptic bombardment, preferably in bursts, and cooperative activity of a number of converging afferent fibers.[50,51,93,99] From the behavioral point of view these conditions must be present at times when an important behavior that leads to reward or punishment is to be reinforced.[63,78,128,131,145] As will be discussed below the cellular events underlying hippocampal SPWs may satisfy these requirements.[25]

The three main variables for the induction of LTP are intensity, frequency, and pattern. The intensity of synaptic drive during the SPW may be estimated by the firing frequency of interneurons, since the discharge rate of fast-firing interneurons is correlated with their depolarization. Long bursts of action potentials above 600/s have been observed in interneurons in association with SPWs.[34] Such high rates of firing have not yet been reported in hippocampal interneurons during theta activity. As LTP magnitude is directly proportional to the depolarization of the postsynaptic membrane,[44,95,99] this finding suggests that the induction of LTP in pyramidal cells is most likely during the SPW-burst.

Another indication of strong synaptic drive during SPW is the presence of "mini"-population spikes riding on the peak of the SPW.[27,110,140] It is relevant to note here that the threshold of LTP is at or near the stimulus intensity required to elicit a population spike.[99,100]

The overall frequency of synaptic activity on a given pyramidal cell during the SPW-bursts is difficult to estimate. The highest frequency in a given afferent fiber is equal to the frequency of action potentials in pyramidal cells during a complex-spike burst of two to seven spikes and is in the range of 50–300 Hz.[120] This repetition rate is similar to the frequency of the "mini"-population spikes of the SPWs (50–200 Hz) and to the optimum frequency range for the induction of LTP.[50] Pyramidal cells often fire complex-spike bursts (i.e. a combination of Na^+ and calcium spikes) during SPWs but they rarely do so during theta-behaviors.[34,137] The time-delayed nature of individual cells during the population burst is probably important in light of the observation that delayed activation of the medial and lateral perforant paths was significantly more effective in the induction of LTP in the dentate gyrus than was simultaneous stimulation of the two inputs.[157] The SPW-associated population burst also meets the "co-activation" requirement of LTP.[12,93,99]

Induction of LTP in the CA1 region and dentate gyrus appears to depend on the activation of voltage-dependent *N*-methyl-D-aspartate (NMDA) receptors.[44,69] Postsynaptic depolarization relieves a magnesium block of the NMDA subtype of glutamate-activated channels. Only when this channel is unblocked can it conduct in response to glutamate released into the synaptic cleft. Pharmacological blockade of the NMDA receptors or direct hyperpolarization of the postsynaptic neuron prevents the occurrence of LTP.[44,95,108] Important enough in the

present context, the occurrence of Ca^{2+} spikes (complex-spike patterns) in CA1 pyramidal cells and neocortical neurons is attenuated during blockade of the NMDA receptors.[1,6] The logical progression of thought is to suggest that LTP might be facilitated during the time-window of the SPW-burst when NMDA receptors may be activated endogenously.

As discussed earlier, SPW-bursts are a consequence of a temporary release from the subcortically-mediated tonic suppression.[23,60] The transient disinhibition may be especially important, because of the empirical findings that LTP is conspicuously robust in the disinhibited hippocampal slice[154] and neocortex[8] and in hippocampal grafts with impaired inhibition.[41]

In summary, complex-spike (burst) firing and large depolarization of a group of pyramidal cells, and convergent coactivation of these neurons during the SPW-population burst, make this neuronal pattern the most likely candidate for producing long-lasting synaptic modifications in the hippocampal circuitry. A formal model of this hypothesis will be elaborated below.

3.1. *Hebb synapses and sharp wave: a new concept*

Hebb[71] proposed that correlated afferent activity and firing of the postsynaptic cell leads to an increase in synaptic efficacy. Several experiments have confirmed a relaxed version of this postulate by demonstrating that pairing of independent weak and strong inputs produced facilitation of the weak input, whereas independent activation of the weak input would not result in such a change.[11,12,84,93]

At present it is unclear whether the enhanced efficacy of a hitherto ineffective afferent system is due to moderate changes in a large number of connections or to large changes at a few synapses. To date all formal models have assumed the existence of the latter.[74,86,96,98]

An essential element in the Hebbian model of association is a teaching input. The teaching or detonator input to a postsynaptic cell possesses two main features: (a) it always discharges the postsynaptic neuron; and (b) it is non-modifiable.[96,98] A major problem with the concept of the teaching input is that individual hippocampal excitatory synapses are both extremely weak and rather unreliable[100,104] and, to date, all synapses examined in the intrahippocampal circuitry have proved plastic.[144]

We suggest that separate detonator synapses neither exist in the hippocampus nor are necessary for synaptic plasticity. Instead, we hypothesize that the strong convergence of excitatory actions on some cells of the neuronal network from otherwise "normal" afferents may produce depolarizations of sufficient magnitude and duration in those neurons and trigger the LTP mechanism. Thus, we conceive the detonator or teaching "synapses" as a collective property of the network and propose that the "strong input" requirements of the Hebbian model may be substituted with the population excitatory events underlying hippocampal SPW.

Furthermore, none of the formal models attributes any significance to the subcortical inputs to the hippocampus. This is biologically a very relevant point since the hippocampus cannot properly function following removal of subcortical afferents.[61,110,113]

It follows from the above that a weak synaptic input can be potentiated by synchronous population events triggered by subcortical disinhibition. In this conceptualization of the LTP the subcortical inputs, which in psychological terms carry information about stress, emotions, drive, motivation and autonomic state of the animal, exert an important permissive action on the formation of new synaptic bonds.

Implicit in the hypothesis that SPW may be a physiological mechanism of LTP are the predictions that conditions which lead to the enhancement of synaptic efficacy should increase the synchrony of the population burst underlying the SPW and, conversely, network bursts mimicking the SPW should induce LTP. These possibilities will be considered in the following sections.

3.2. *Long-term potentiation of hippocampal sharp wave-bursts*

The largest amplitude SPW (2.5 mV) can be recorded from the stratum radiatum of CA1 at the terminal zone of the Schaffer collaterals.[34] The amplitude and duration of the SPW reflect the degree of synchrony of CA3 pyramidal neurons. We hypothesized that an increase of the synaptic efficacy in the recurrent collateral system of CA3 and the Schaffer collateral–CA1 connection by LTP would also be reflected in the spontaneous activity of the cell population. Conditioning high-frequency stimulation of the CA3 region induced LTP of both evoked population spike and extracellular postsynaptic potential. Parallel with the enhancement of the evoked responses the incidence and amplitude of SPWs also increased and their duration decreased.[24] The induced changes lasted for several days. This was the first demonstration that LTP effects are also reflected in the spontaneous activity of the hippocampus. We interpreted this finding by assuming that afferent tetanization increased the efficacy of the recurrent and Schaffer collateral synapses of CA3 pyramidal cells which, in turn, lowered the threshold of the SPW-initiating burst and increased its incidence and synchrony by allowing faster spread of polysynaptic excitation in the CA3 region.

This hypothesis is supported by recent experiments carried out in the *in vitro* slice preparation. Miles and Wong[105] made recordings from pairs of CA3 pyramidal cells in the hippocampal slice preparation. Following high-frequency conditioning trains, the synaptic efficacy of polysynaptic excitatory connections between cell pairs increased considerably. In a conceptually similar experiment Higashima[72] induced evoked bursts in the CA3 region by repeatedly

tetanizing the stratum radiatum. The triggered bursts spread across the CA3 region and test stimuli delivered to either the tetanized or different loci were equally effective in triggering the bursts, and the latency of the evoked burst was shortest at the site of tetanization. This finding demonstrates that the triggered population bursts were generated at a focus near the tetanization site and propagated to the neighboring areas.

To summarize, an essential consequence of the LTP in the CA3 region is an increased probability and tighter synchrony of network bursts.

3.3. *Afferent patterns determine the structure of population burst*

In an attempt to answer the question as to whether the same or different sets of neurons contribute to successive SPW-bursts, we tried to influence the structure of the population bursts by afferent stimulation. We have described elsewhere that in rats with fimbria–fornix lesion, large-amplitude (up to 8 mV) short-duration EEG spikes occur spontaneously and their incidence may be influenced by stimulation of the perforant path.[39,40] We used multichannel recordings from the CA1 area to study how high-frequency trains affect the morphology of SPWs along the longitudinal axis of the hippocampus.

Figure 8 illustrates such an experiment. First, evoked potentials were recorded in response to perforant path stimulation. Next, high-frequency conditioning trains were delivered to the perforant path and the spontaneously occurring EEG spikes were detected following the trains. We found that as a result of the high-frequency stimulation the shape and spatial distribution of the EEG spikes became very similar to the evoked responses. A major difference between the evoked and spontaneous patterns was the lack of the volume-conducted dentate potential in the spontaneous EEG spikes. These findings are interpreted by assuming that the perforant path conditioning trains led to the potentiation of a subgroup of CA3 neurons which, in turn, became the "initiators" of the subsequently occurring population bursts.

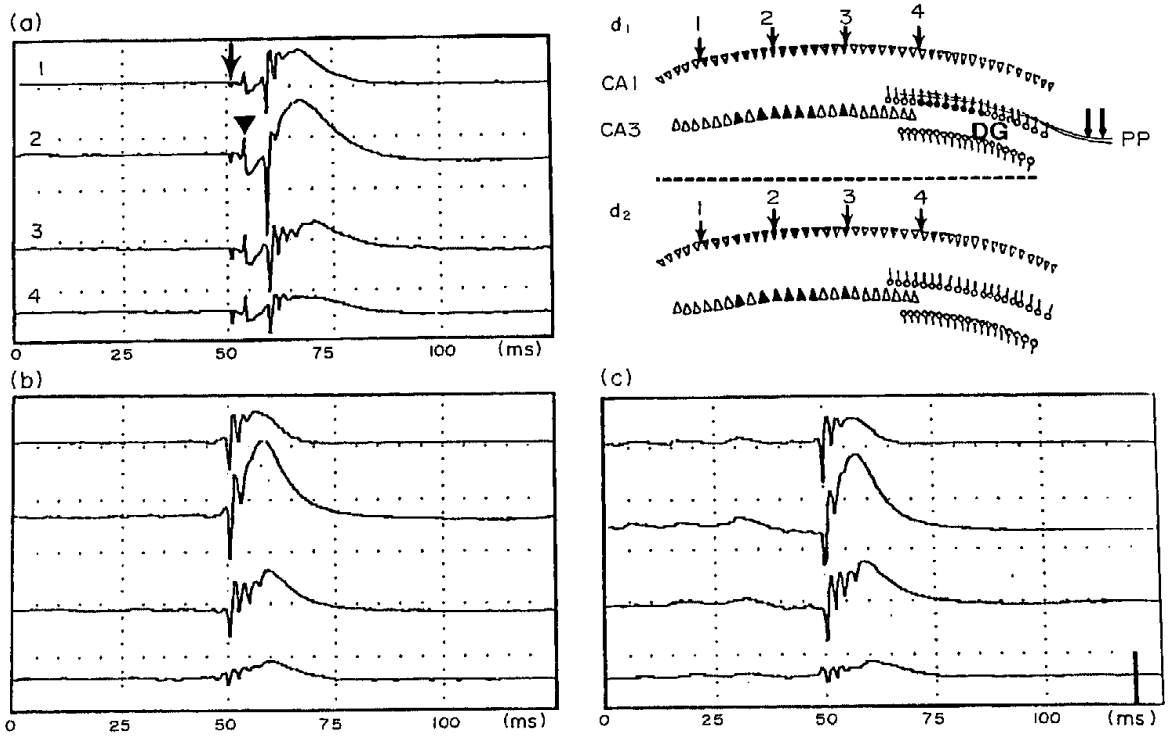

Fig. 8. Stimulation-induced EEG spikes. Recording electrodes (1–4) were positioned in the pyramidal layer of CA1 along the longitudinal axis of the hippocampus.[38] Distance between electrodes: 500 μm. In this animal the fimbria–fornix was removed by aspiration.[40] Single pulse stimulation of the perforant path (arrows in a and d_1; PP) evoked monosynaptic population spikes in the dentate gyrus and trisynaptic responses in CA1. Triangle in a indicates volume-conducted population spike from the dentate gyrus. Following high frequency tetanization of the perforant path (8 times 200 Hz, 100 ms bursts), large-amplitude spontaneous EEG spikes occurred after the trains (b: 1 min; c: 5 min). Note virtual identical configuration of the evoked responses (a) and spontaneously occurring EEG spikes (b, c) in all four leads. Note also the absence of the dentate component in the EEG spikes. d_1 and d_2. Possible circuit diagram of the events in a–c. Single pulse stimulation of a subset of perforant path (PP in d_1) sequentially activated subgroups of granule cells, CA3 and CA1 pyramidal neurons (black circles and black triangles). Tetanization of PP induced heterosynaptic potentiation of the recurrent axon collaterals of the CA3 cell group. These potentiated CA3 pyramidal cells then served as "initiator" neurons of the subsequent spontaneous population bursts (d_2). Postsynaptic activation of CA1 pyramidal neurons (mainly in the vicinity of electrode 2) by the bursting CA3 cells resulted in EEG spikes. Potentiation of a subpopulation of CA3 pyramidal neurons (initiator cells) is thus assumed to be responsible for triggering the uniform EEG spikes.

The mechanism of how high-frequency activation of the perforant path input leads to the potentiation of CA3 pyramidal cells remains to be elucidated. The train-induced postsynaptic depolarization effect of CA3 pyramidal cells might have occurred disynaptically via the granule cells or via the direct perforant path–CA3 pyramidal neuron synapse.[28] It is not clear, however, how either of these effects leads to the potentiation of the recurrent axon collaterals of CA3 cells. Nevertheless, heterosynaptic potentiation of evoked responses has been reported previously *in vivo* and in the hippocampal slice preparation.[2,107,121,159] Recently, Higashima and Yamamoto[73] reported that mossy fiber stimulation evoked both an early and a late synaptic response and both responses showed long-term enhancement following tetanization of the mossy fibers. Importantly enough, only the late response showed heterosynaptic potentiation when tested by the non-tetanized test input in the stratum radiatum. LTP of the late response also occurred in slices where the early response did not display potentiation. The authors hypothesized that long-lasting enhancement of the late response resulted from a modified interaction among postsynaptic CA3 neurons.

Based on the above findings we hypothesize that converging high-frequency activation of the CA3 pyramidal neurons by the granule cells might transiently lead to the potentiation of a subset of CA3 pyramidal cells which, in turn, may serve as trigger or "initiator" cells of subsequent, spontaneously occurring SPW-population bursts.

3.4. *Long-term potentiation induced by sharp wave-like bursts*

In order to explore the possible involvement of SPWs in physiologically occurring LTP, we artificially induced population bursts in the hippocampal slice preparation. Population bursts in the CA3 region were triggered by single pulse stimulation of the Schaffer collaterals in the presence of local application of bicuculline onto the CA3 pyramidal cells. The single volleys evoked a series of small-amplitude spikes in the CA3 region, similar to the "mini"-population spikes occurring during the SPW. The population bursts in CA3 induced a large increase in the population spike of the test responses in CA1 (Fig. 9).[37] The potentiation outlasted the local effects of bicuculline on the CA3 pyramidal cells and thus represented a true long-term synaptic change.

In a technically similar, but conceptually different experiment LTP could be induced by single pulses in the CA1 region when the whole slice was perfused with picrotoxin.[3] The prerequisite for the occurrence of LTP was the presence of multiple population spikes evoked by the electrical stimulus. Multiple population bursts in CA3 and consequent LTP could also be induced by perfusing the slice with kainic acid.[15]

Since highly synchronous bursts of neuronal activity are known to occur during epileptic discharges we have recently questioned whether propagation of epileptic activity might be explained by LTP-like changes. Afterdischarges were evoked by either picrotoxin or low-frequency (5 Hz) stimulation of the perforant path. Evoked potentials in the dentate gyrus were depressed immediately after the seizure but they were significantly larger between 8 and 20 h after both procedures.[31]

Apparently, more direct tests are required to provide firm evidence that SPW-associated bursts do indeed induce plastic changes in the hippocampal circuitry. Nevertheless, these pilot experiments indicate that evoked population bursts produce enhancement of synaptic efficacy comparable to the stimulation-induced LTP.

4. LONG-TERM POTENTIATION IN THE DENTATE GYRUS: ARE THE RULES DIFFERENT?

As discussed above, granule cells are relatively quiescent during immobility and consummatory behaviors but show a several-fold increase during exploratory behaviors associated with hippocampal theta waves (Fig. 10).[34,36,122]

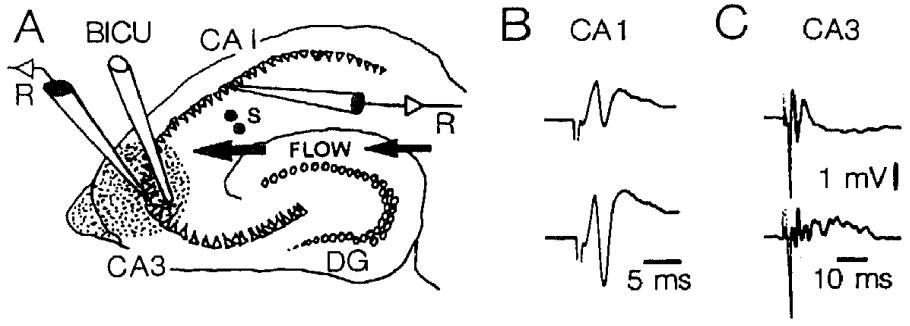

Fig. 9. LTP induced by population bursts. (A) Diagram of a hippocampal slice showing the location of stimulating (S) and recording (R) electrodes and the bicuculline-containing micropipette (BICU). The stippled area shows the typical extent of bicuculline diffusion. (B) Averages of eight evoked responses before (above) and 20 min after (below) bicuculline application to the CA3 region. Potentiation was present up to 90 min. (C) Antidromic responses in CA3 before (above) and during (below) bicuculline application. Note repetitive population spikes. (Taken from Ref. 37.)

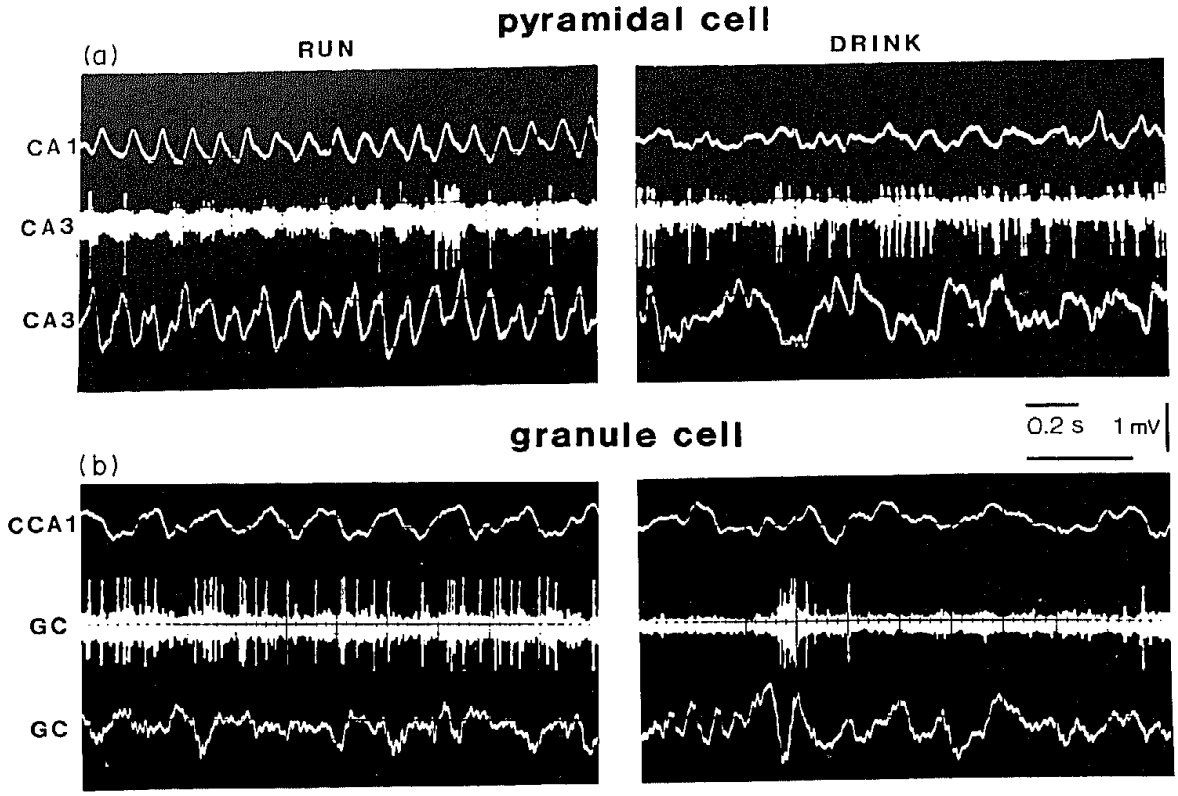

Fig. 10. Behavior-dependent discharges of pyramidal neurons and granule cells. (a) Fixed electrode in stratum oriens of CA1 (first trace) and microelectrode in the CA3 pyramidal layer (second and third traces). Note increased firing frequency of the pyramidal neuron during drinking. (b) Recording from a granule cell in a rat with unilateral fimbria–fornix lesion.[34] CCA1, fixed electrode in stratum oriens of CA1, contralateral to the lesion. Note high-frequency discharge of the granule cell during running. Because all subcortical and commisural inputs to the dentate gyrus had been removed by the lesion the frequency increase during running could be brought about only by the perforant path.

The dentate gyrus is an important relay between the neocortical input and the CA3 field. It is not understood how the spatial and other preprocessed sensory information, carried by the perforant path input, is transformed by the rhythmic firing granule cells to result in spatial and conditioned firing of pyramidal cells. Granule cells provide very little information about the animal's location in the environment.[101]

LTP in the dentate gyrus is most efficient when conditioning trains are delivered during theta-associated behaviors (i.e. when granule cells fire at a high rate) and LTP is either absent or shows extremely large variability when the trains are given during slow wave sleep.[21,22,91] Furthermore, conditioning stimuli presented at the positive peak of local theta, the preferred phase for granule cell firing,[34,35,57] have been found to induce larger LTP as compared to identical trains presented at the negative peak.[114]

LTP in dentate gyrus appears to depend strongly on subcortical inputs to the dentate gyrus.[87] Damage or pharmacological blockade of the serotoninergic[18] and the noradrenergic[134] afferents impairs LTP in both the dentate gyrus and at the mossy fiber–CA3 pyramidal cell synapse.[76]

Following complete subcortical deafferentiation of the hippocampus, LTP is lost permanently in the dentate gyrus[32] but LTP in CA1 does not appear to be affected[134] (Nicoll and Buzsáki, unpublished observations; Buzsáki and Haas, unpublished observations).

Several recent papers report maximum effects on LTP when tetanic trains are repeated at 200 ms also in the CA1 region.[88,123,135] Since the repetition rate of SPWs during an SPW-burst is also 100–200 ms (Fig. 3), these findings equally support the SPW mechanism in this region.

The above review of the physiological discharge patterns of the different hippocampal cell types in relation to LTP suggests that hippocampal SPWs are the best candidate for an LTP mechanism in CA1–CA3 regions, but that the conditions for plastic changes in the dentate gyrus and granule cell–CA3 pyramidal cell synapse might be more favorable during exploratory behaviors associated with theta activity.

5. TWO-STAGE MODEL OF HIPPOCAMPAL LONG-TERM POTENTIATION

We suggest that the behavior-dependent electrical changes in the hippocampus (theta and SPW-associated states) might subserve a two-stage process of information storage. In essence, we hypothetize that information is deposited in a relatively labile form during exploratory activity (theta behaviors) and the labile trace is converted into a long-lasting form at the termination of exploration (i.e. during

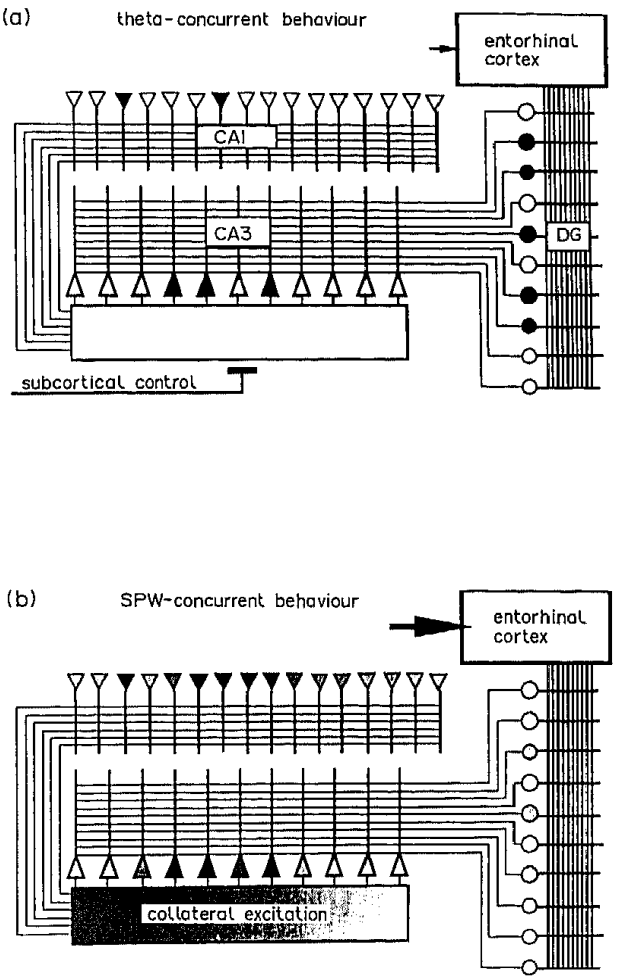

Fig. 11. Two-stage model of hippocampal memory storage. The static schemes represent neuronal information transfer just before termination of exploratory activity (a, theta-state), and the potentiation effect of SPW state (b). (a) During theta behavior the parallel entorhinal input activates a subset of granule cells (black circles) which fire at a higher rate than the rest of the granule cell population. The high-frequency firing and convergence of these cells on CA3 pyramidal cells (black triangles) is sufficient to produce a weak, decaying heterosynaptic potentiation in these pyramidal neurons. The discharging CA3 pyramidal neurons may drive some CA1 pyramidal cells (black triangles). Recurrent collateral excitation in the CA3 region is suppressed by the subcortical inputs, mainly via feed-forward excitation of inhibitory interneurons (not shown). (b) After the termination of the exploratory (theta) state, subcortical control releases recurrent collateral excitation in the CA3 neuronal network (SPW state). The initiator cells (black triangles) of the population bursts are those neurons which were potentiated last during the exploratory state (i.e. the ones with the highest excitability). The excitation wave spreads from the initiator cells to the progressively less excitable ones, i.e. to those cells which were potentiated at progressively earlier times prior to the termination of exploration. During the SPW-concurrent population burst a relatively large percentage of CA3 neurons will be recruited. The maximal effect of the reverberating excitation is converged on the initiator cells and progressively less convergent excitation is present on those cells which were potentiated at earlier epochs of the exploration. The converging excitation is sufficient to induce long-term enhancement of synaptic efficacy in the initiator cells and in their targets in CA1. The large arrow in (b) indicates stronger hippocampal excitatory drive on the entorhinal cortex neurons during SPW-population bursts relative to theta states.

SPW states). Viewed from this perspective both theta and SPW states are obligatory for normal memory trace formation (Fig. 11).

Stage 1. *Labile form of memory trace*—convergence of excitatory inputs from the fast-firing granule cells on CA3 pyramidal neurons during theta-associated behavioral states produces a weak and transient heterosynaptic potentiation of CA3 pyramidal cells. Subject to subcortical influences.

Stage 2. *Long-lasting form of memory trace*—long-term modification of synaptic efficacy is brought about by the SPW-population bursts at the termination of theta behaviors. The highly synchronous population bursts in CA3 will result in long-term enhancement of synaptic efficacy in CA3 and in some of their CA1 target neurons.

Specificity of information storage is ensured by the demonstrated mechanism that (a) the weakly potentiated CA3 cells will become the initiator neurons of the subsequent SPW-associated population bursts and by a hypothesized mechanism that (b) the initiator cells will receive maximum convergence of excitation during a given SPW-burst.

To illustrate our point consider the following example. A rat is moving about in a maze. Information about events or spatial cues is fed into the hippocampal formation via the perforant path, mainly to the dentate granule cells. Since only a portion of neurons is activated by the environmental events in the entorhinal cortex, a subpopulation of granule cells, on which the afferents of the active cells terminate, will be excited significantly more strongly than their neighbors. In the dentate gyrus the information (e.g. space) is coded in a parallel fashion, i.e. in a set of neurons, therefore observing the activity of individual granule cells will not reveal the rat's position in space. Convergence of neuronal impulses on CA3 pyramidal cells and the further convergence of the active CA3 neurons on a subset of CA1 pyramidal cells will result in neurons whose discharge patterns will reveal the complexity of the environmental stimuli on the animal (e.g. spatial units).

The selectively higher firing rate of a set of granule cells during exploration will result in a weak potentiating effect in some CA3 pyramidal cells on which the mossy terminals of the information carrying granule cells converge. The higher the discharge frequency of these particular granule cells and the longer they fire, the stronger the potentiation in their target pyramidal cells will be. As the environmental events change or different spatial cues are noticed, different sets of entorhinal inputs will activate differential subgroups of granule cells and consequently different sets of pyramidal cells will be potentiated. As a result, events that occurred later during the exploratory period, and items the animal investigated longer, will have the most efficient potentiating effects at the termination of the exploratory-orienting (theta) state. Potentiating effects of events and cues which occurred earlier during the

information-collecting exploratory bout will progressively dissipate. The weak potentiating effects are strongly influenced by subcortical control mechanisms at this stage.

We suggest that creation of the long-lasting form of memory trace begins at the termination of the exploratory (theta) state, with the onset of hippocampal SPW-bursts. A key feature of this process is a structurally–functionally controlled reverberation of excitation in the CA3 region (auto-association). As discussed earlier, the initiator cells[103] of the self-generating population bursts are the very ones which were most strongly potentiated before the termination of the exploratory state.

We assume that recurrent collateral excitation in the CA3 region spreads in a hierarchical fashion: the most excitable cells fire first followed by less excitable ones, that is in the reverse order to that in which they were potentiated during exploration (Fig. 12). As the population burst spreads the maximal effect of the reverberating excitation will converge on the initiator cells and progressively less convergent excitation will occur on those neurons which were more weakly potentiated during exploration; again in the reverse order. These latter mechanisms ensure that only those neurons which carry information about the most recent events will be potentiated.

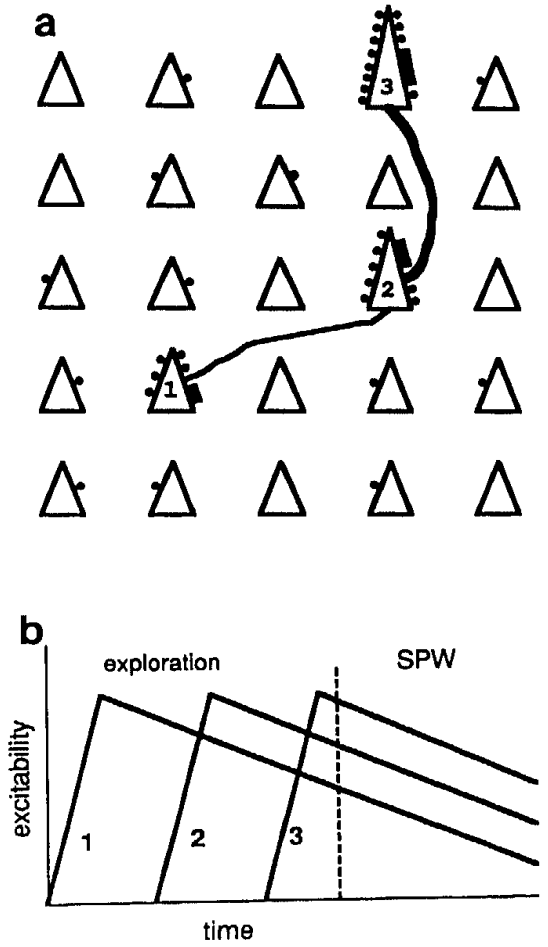

Fig. 12. The hierarchical organization of the SPW-associated population burst depends on the recent history of the CA3 neuronal network. (a) The height of the pyramidal cells is proportional to their excitability. The excitability in cells 1, 2 and 3 is weakly potentiated by the mossy fiber terminals (black rectangles) by successive events during exploration. The graph in (b) illustrates the decaying potentiation of neurons 1, 2 and 3. The population burst is initiated by the most excitable neuron (3) and the excitation wave spreads to the progressively less excitable ones (2, 1 and unlabeled cells). A large portion of the neurons will eventually be recruited by polysynaptic reverberation. The recurrent converging excitation (dots) will be maximum on cell 3, followed by cells 2 and 1, and sufficiently strong to induce LTP in these cells.

The function of the second stage in the CA3 region is, therefore, to select a group of neurons (burst-initiators) and to strengthen the synaptic connections between them. A subset of neurons in CA1 on which the initiator cells of the CA3 population burst converge, will be depolarized substantially more strongly during the SPW-bursts than their neighbors and the Schaffer synapses of these neurons will undergo LTP. These CA1 cells are, of course, the same neurons which discharged maximally during the exploratory stage. For example, at the termination of exploratory behavior a particular set of spatial units continues to discriminate the rat's position, but now firing of these cells will coincide with SPW-correlated population bursts. Due to the powerful depolarization of these spatial units, brought about by the population burst, their Schaffer synapses may undergo long-term potentiation. In the light of the known anatomical–physiological organization of the hippocampal circuitry, it is hard to explain how the entorhinal cortex-mediated neuronal information produces synaptic modification in CA1 without the SPW-population burst. The two-stage model therefore assigns an important active role to the CA3 region.

Although the intact hippocampus is essential for depositing new memories, it is not itself a memory store.[80,106,132] The mechanism of the SPW-burst, however, may aid enhancement of synaptic bonds in target structures of the hippocampus. We have demonstrated the high fidelity of the reafferent copy that the hippocampus returns to the entorhinal cortex (Fig. 5). The intrahippocampally generated SPW-population burst may therefore serve to induce sufficiently large depolarization and to trigger LTP in the neurons of the entorhinal cortex. From this perspective, the hippocampus is conceived as an association–feedback device which potentiates the neocortical representations.

The above-outlined sequential potentiation mechanisms are assumed to ensure that discharge of a given set of entorhinal neurons during subsequent visits to the same part of the maze (recall) will reactivate the same subsets of neurons in CA3 and CA1. Neuronal firing during the SPW-associated burst, therefore, is precisely determined by the recent past of the neural network. The rules of burst initiation and reconvergent excitation, subserved by the anatomical–physiological organization of the CA3 region, ensure that the synchronized events carry biologically meaningful information.

5.1. *Strengths and weaknesses of the two-stage model*

The rule of functional hierarchy expands the storage capacity of the neural network enormously. The model also provides an explanation of the spatial–temporal continguity of memory,[68,131,145] i.e. how events and items with spatial and temporal proximity are translated into interpretable physiological activity. The decaying nature of the mossy fiber-induced potentiation in CA3 pyramidal cells may offer a structure-independent explanation of the limited capacity of working memory.[113] The hypothesis of the two-stage process of LTP offers new insights into the biological relevance and information storing capacity of population events in anatomically–physiologically organized neuronal networks. Above all, it offers an explanation of the utility of irregularly bursting neuronal states, which occupy a large portion of the brain's computing time.

Though the model is firmly grounded in current knowledge of neuroanatomy and physiology, it remains long on speculation and short on data. To date, no direct experimental evidence is available to support the hypothesis that the creation of burst initiator cells is brought about by the mechanism of excitatory reconvergence. Furthermore, despite the strong similarities between the neuronal events during an SPW-population burst and the experimental conditions required for the induction of LTP, it remains to be demonstrated that LTP does indeed occur during physiological conditions.

Recent experiments *in vitro* and *in vivo* suggested that synaptic modification in the hippocampus occurs mainly during theta activity. This hypothesis is based on empirical findings showing that robust LTP is obtained if tetanic trains are delivered at 100–200 ms intervals (theta frequency).[88,123,135] We emphasize that these findings are compatible with our model because (a) when SPWs occur in bursts the typical inter-SPW interval is 100–200 ms, and (b) reactivation of the burst-initiator cells during the population event may be delayed to the end of the SPW (i.e. 100–150 ms). Indeed, the finding that single pulse-train pairs at this interval are especially effective in inducing LTP ("prime-burst" potentiation[123]) supports the hypothesis of population reactivation of burst initiator cells.

6. A NOTE ON SLEEP

The dichotomy of the hippocampal electrical patterns in the awake animal (theta versus SPW states), is also present during sleep. Indeed, the highest incidence of SPWs occurs in slow wave sleep[26,70,82,110,138,151] and the most regular hippocampal theta is present during the "active" or paradoxical phase of sleep.[16,151]

Sleep deprivation studies, carried out on humans and experimental animals, provide strong support for the importance of sleep on memory consolidation.[54,56,77] Most of these studies stress the pivotal role of the paradoxical (rapid eye movement) stage of sleep mainly because of the observation that most dream episodes occur during the paradoxical stage.[47,48]

Our neurophysiological model of memory trace formation lends further support for the importance of the sleep process in memory consolidation and provides a possible physiological basis of the consolidation mechanism. It directly predicts that retention of a task will be significantly better if followed by a sleep episode, due to the abundance of SPW-bursts during slow wave sleep. The functions of paradoxical sleep might be to reload the hippocampus with the information of the preceding learning episode and to refresh the leading role of the initiator cells in SPW-concurrent population bursts during subsequent slow wave sleep epochs. To summarize, the two-stage model equally emphasizes the importance of both sleep stages as well as their physiological sequences.

7. SHARP WAVE-BURSTS AND INTERICTAL SPIKES OR WHY IS THE HIPPOCAMPUS THE MOST EPILEPSY-PRONE STRUCTURE IN THE BRAIN?

Perhaps the late Graham Goddard was the first to suspect that similar plastic mechanisms might support the formation of the engram and the generation of epileptic activity[64,65] based on the observation that repeated LTP-inducing trains, sufficient to induce afterdischarges, may result in kindling.[66,97,118]

Interictal spikes are a major electroencephalographic manifestation of various forms of epilepsies. Generally, three factors are considered to be essential for epileptic synchronization. First, cortical neurons may intrinsically generate bursts of action potentials (Na^+ spikes superimposed on Ca^{2+} spikes). Second, recurrent excitatory connections should exist that are powerful enough so that bursting activity may spread between synaptically connected neurons. Third, inhibition within the local neuronal circuit must be adequately attenuated to allow spread of excitation between synaptically connected neurons.[117,146,147,148,158] Recently, the cellular mechanisms of network synchronization have been thoroughly investigated in the *in vitro* hippocampal slice preparation. These studies indicate that interictal spikes are initiated in the CA2–CA3 region of the penicillin-treated hippocampus and the synchronous bursts induce temporally summated "giant" excitatory postsynaptic potentials in the apical dendrites of CA1 pyramidal cells which may trigger action potentials in their cell bodies.[62,81,125,146,158] Thus, from this brief overview it is apparent that the same neuronal machinery might be involved in generating physiologically occuring SPWs and epileptic interictal spikes, since bursting pyramidal cells, collateral excitation, and temporal release from tonic inhibition, are the main elements of both neuronal patterns.

A key issue that requires elucidation is to reveal

what mechanisms limit the spread of population synchrony during SPW-bursts. Under physiological circumstances hitherto unknown homeostatic mechanisms may decrease the synchrony of bursting pyramidal neurons and/or limit the recruitment of further cells during a population burst. Both the tightness of synchrony and collateral spread of excitation may be increased by the mechanism of LTP[24,105] and enhancement of synchrony may lead to more efficient LTP in the participating neuronal groups. This self-generating mechanism may continue until the LTP mechanism is saturated[99] and fully developed interictal spikes appear in the hippocampal record. The newly formed excitatory bonds may become sufficiently strong so that during subsequent exploratory (theta) bouts the entorhinal volleys will no longer be capable of setting up initiator cells for SPW-bursts. As a result a circumscribed set of the neuronal population (the "focus") will always be responsible for triggering a population burst.

The two-stage model offers an explanation of why epileptic activity is often associated with memory problems.[90] It follows from the model that deposition of a new memory trace requires new sets of initiator cells in the CA3 region and this flexibility may be lost in the epileptic hippocampus due to the stationary, low-threshold epileptic focus. This interference hypothesis finds support in recent empirical data. McNaughton *et al.*[102] tested the learning capabilities of rats following LTP-inducing trains delivered to the perforant path. Rats with daily LTP trains remained significantly inferior relative to their non-stimulated controls. We suggest that the tetanizing trains might have produced a subpopulation of burst-initiator cells (e.g. Fig. 6), and interfered with the candidate initiator cells that were produced during the exploratory phase of the task.

We conclude that the hippocampus is a predilected structure for epilepsy because it has "built-in" mechanisms for both population synchrony and synaptic plasticity. We suggest that epileptic activity reflects the deterioration of finely tuned homeostatic mechanisms that regulate the magnitude of population synchrony under physiological conditions.

8. FUTURE PERSPECTIVES

The significance of electrically induced synaptic plasticity (LTP) ultimately rests on its possible physiological role in the intact nervous system. During the past decade a great deal of factual knowledge has been accumulated on the synaptic, biophysical, pharmacological and molecular properties of the mechanisms that govern the induction, expression and maintenance of LTP. The demonstration that LTP is generated endogenously and subserves a mnemonic process, however, remains a challenge for future studies. A more direct approach, the one used in this review, is to investigate which physiologically occurring neuronal patterns might satisfy the empirically established criteria of synaptic modification.

Although several components of the hypothesized two-stage model of memory trace formation are supported by experimental evidence, verification of several of its predictions remains to be elucidated. Future studies should address: (1) the nature of heterosynaptic potentiation in the CA3 region; (2) the formation of burst-initiator neurons during a learning process and their altered discharge patterns during subsequent consummatory and sleep states; (3) the mechanisms of reconvergent excitation of the initiator cells during population bursts; (4) the factors that limit the spread of synchronized neuronal activity during physiologically occurring population events; (5) the fidelity of the hippocampus-mediated reafferent copy in associational areas of the neocortex and the role of hippocampal SPW-bursts in modifying their neuronal patterns; and (6) the influence of behavioral, pharmacological manipulations and lesions affecting the normal sequence of theta and SPW states on learning and memory.

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