GABAergic Modulation of Hippocampal Population Activity: Sequence Learning, Place Field Development, and the Phase Precession Effect

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Wallenstein, Gene V. and Michael E. Hasselmo. GABAergic modulation of hippocampal population activity: sequence learning, place field development, and the phase precession effect. *J. Neurophysiol.* 78: 393–408, 1997. A detailed biophysical model of hippocampal region CA3 was constructed to study how GABAergic modulation influences place field development and the learning and recall of sequence information. Simulations included 1,000 multicompartmental pyramidal cells, each consisting of seven intrinsic and four synaptic currents, and 200 multicompartmental interneurons, consisting of two intrinsic and four synaptic currents. Excitatory rhythmic septal input to the apical dendrites of pyramidal cells and both excitatory and inhibitory input to interneurons at theta frequencies provided a cellular basis for the development of theta and gamma frequency oscillations in population activity. The fundamental frequency of theta oscillations was dictated by the driving rhythm from the septum. Gamma oscillation frequency, however, was determined by both the decay time of the γ-aminobutyric acid-A ($GABA_A$)-receptor-mediated synaptic current and the overall level of excitability in interneurons due to α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid and *N*-methyl-D-aspartate (NMDA)-receptor-gated channel activation. During theta population activity, total $GABA_B$-receptor-mediated conductance levels were found to gradually rise and fall in rhythmic fashion with the predominant population frequency (theta rhythm). This resulted in periodic $GABA_B$-receptor-mediated suppression of excitatory synaptic transmission at recurrent collaterals (intrinsic fibers) of pyramidal cells and suppression of inhibitory synaptic transmission to both pyramidal cells and interneurons. To test the ability of the model to learn and recall temporal sequence information, a completion task was employed. During learning, the network was presented a sequence of nonorthogonal spatial patterns. Each input pattern represented a spatial ''location'' of a simulated rat running a specific navigational path. Hebbian-type learning was expressed as an increase in postsynaptic NMDA-receptor-mediated conductances. Because of several factors including the sparse, asymmetric excitatory synaptic connections among pyramidal cells in the model and a sufficient degree of random ''background'' firing unrelated to the input patterns, repeated simulated runs resulted in the gradual emergence of place fields where a given cell began to respond to a contiguous segment of locations on the path. During recall, the simulated rat was placed at a random location on the previously learned path and tested to see whether the sequence of locations could be completed on the basis of this initial position. Periodic $GABA_B$-receptor-mediated suppression of excitatory and inhibitory transmission at intrinsic but not afferent fibers resulted in sensory information about location being dominant during early portions of each theta cycle when $GABA_B$-receptor-related effects were highest. This suppression declined with levels of $GABA_B$ receptor activation toward the end of a theta cycle, resulting in an increase in synaptic transmission at intrinsic fibers and the subsequent recall of a segment of the entire location sequence. This scenario typically continued across theta cycles until the full sequence was recalled. When the $GABA_B$-receptor-mediated suppression of excitatory and inhibitory transmission at intrinsic fibers was not included in the model, place field development was curtailed and the network consequently exhibited poor learning and recall performance. This was, in part, due to increased competition of information from intrinsic and afferent fibers during early portions of each theta cycle. Because afferent sensory information did not dominate early in each cycle, the current location of the rat was obscured by ongoing activity from intrinsic sources. Furthermore, even when the current location was accurately identified, competition between afferent and intrinsic sources resulted in a tendency for rapid recall of several locations at once, which often lead to inaccuracies in the sequence. Thus the rat often recalled a path different from the particular one that was learned. $GABA_B$-receptor-mediated modulation of excitatory synaptic transmission within a theta cycle resulted in a systematic relationship between single-unit activity and peaks in pyramidal cell population behavior (theta rhythm). Because presynaptic inhibition of intrinsic fibers was strongest at early portions of each theta cycle, single-unit firing usually started late in a cycle as the place field of the associated cell was approached. This firing typically advanced to progressively earlier phases in a theta cycle as the place field was traversed. Thus, as the rat moved through successive locations along a learned trajectory during completion trials, place cell firing gradually shifted from late phases of a theta cycle, where future locations were ''predicted'' (intrinsic information dominated), to early phases of a cycle, where the current location was ''perceived'' (afferent sources dominated). This result suggests that the GABAergic modulation of temporal sequence learning may serve as a general framework for understanding navigational phenomena such as the phase precession effect.

INTRODUCTION

For some time now, long-term potentiation (LTP) has been the guiding model in our understanding of the cellular mechanisms supporting learning and memory in the CNS (Bliss and Collingridge 1993; Bliss and Lomo 1973). Indeed, theoretical models known as associative memory networks typically rely on Hebbian-type learning (in which the synaptic efficacy between a pre- and postsynaptic cell increases in proportion to their coactivation) (Hasselmo 1993; Hasselmo et al. 1995; Levy 1989; Marr 1971; McNaughton and Morris 1987), with primary justification from experimental studies demonstrating LTP induction consistent with this conceptual model (e.g., Kelso et al. 1986; Wigstrom et al. 1986). These models are endowed with the ability to learn static patterns of information stored across

the spatial extent of the network and recall them during completion tasks in which a degraded version of the full pattern is presented (see Hasselmo 1995). Hebbian-type learning in conjunction with a pronounced anatomic background of recurrent excitatory synapses has served as a foundation for many models of associative memory in hippocampal region CA3 (Hasselmo et al. 1995, 1996; Levy 1996; Wallenstein and Hasselmo 1997a,b).

A problem becomes apparent, however, when one attempts to store and recall temporal patterns of information in associative networks with the use of realistic approximations of LTP. Experimental observations have shown that LTP of a synapse occurs preferentially when a presynaptic cell fires before postsynaptic cell activation within a time window of ~50 ms or less (Larson and Lynch 1989; Larson et al. 1986; Levy and Steward 1983). How, then, are temporal associations learned in the hippocampus if the time interval spanning two distinct events is greater than this value? As has been remarked on elsewhere, most hippocampal models of sequence learning have failed to address this issue without relying on mechanisms unsupported by existing physiological observations (Skaggs and McNaughton 1995). The question of how temporal sequences are learned and recalled in the hippocampus provides a general framework for asking related, but more specific, questions. For example, if one makes the analogy between a particular pattern in a temporal sequence given to a model network and a rat's spatial location in a maze during a memory task, then the temporal sequence of such patterns is analogous to the rat's path through space. Thus understanding how temporal sequences are learned and recalled in biophysically realistic models of the hippocampus may shed light on questions concerning how organisms remember navigational routes. A physiological basis for solving this problem may reside in several lines of converging evidence involving the modulation of cellular behavior in the hippocampus by γ-aminobutyric acid (GABA) and how this modulation may alter firing activity on a time scale comparable with the endogenous 4- to 9-Hz theta rhythm.

Recent electrophysiological experiments have shown that the $GABA_B$ receptor agonist baclofen selectively decreases the amplitude of excitatory postsynaptic potentials (EPSPs) in hippocampal CA1 pyramidal cells induced by Schaffer collateral stimulation but leaves perforant path transmission unaltered (Ault and Nadler 1982; Colbert and Levy 1992). Colbert and Levy (1992) demonstrated (in vitro, after removal of the dentate gyrus and region CA3) a decrease in the population EPSP slope in stratum radiatum in response to stimulation of the Schaffer collateral under bath application of baclofen. Contrasting this, baclofen had no significant effect on the population EPSP slope when the perforant path was stimulated. Thus connections between pyramidal cells within the hippocampus (intrinsic and association fibers) are modulated by $GABA_B$ receptor activation, whereas sensory signals arising from afferent fibers outside this cortical area are left relatively unaffected. Consequently, the relative contribution of information from inside and outside the hippocampus is shaped by this modulation. Suppression of excitatory synaptic transmission by baclofen has also been shown in the piriform cortex, where a consistent relationship between paired-pulse facilitation and the amount of suppression has suggested a presynaptic mechanism (Tang and Hasselmo 1994). Potashner (1979) has in fact shown that the evoked release of ^{3}H-glutamate in guinea pig cortical slices is reduced by baclofen, possibly through the activation of $GABA_B$ autoreceptors.

Baclofen has also been found to reduce inhibitory postsynaptic potentials (IPSPs) in hippocampal (Kamiya 1991) and neocortical (Howe et al. 1987) slice preparations. As is the case for EPSP suppression, the suppression of IPSPs is possibly due to activation of presynaptic $GABA_B$-receptor-mediated K^+ currents that hyperpolarize terminal endings of sufficient magnitude to decrease the Ca^{2+} influx required for quantal release. Consistent with this scenario, it has recently been shown that high-frequency stimulation in hippocampal region CA1 caused a reduction in GABA transmitter release due to an action at $GABA_B$ autoreceptors (Davies et al. 1990). Indeed, it has been suggested that this mechanism may also be responsible for the baclofen-induced suppression of fast $GABA_A$-mediated IPSPs in neocortical slice preparations (Howe et al. 1987). However, it should be noted that these observations do not preclude additional biophysical mechanisms that may reduce internal Ca^{2+} concentrations. For example, Wu and Saggau (1995) have demonstrated a suppression of the CA1 field EPSP that may be caused by a more direct presynaptic $GABA_B$-receptor-mediated block of Ca^{2+} channels. In this scenario, a decrease in internal Ca^{2+} concentration is due to active coupling of $GABA_B$ autoreceptors and Ca^{2+} channels rather than a consequence of the voltage dependence of the latter.

The suppression of excitatory and inhibitory synaptic transmission by $GABA_B$ receptor activation is an interesting effect in the hippocampus, because it is possible that such modulation occurs in a rhythmic fashion during theta activity. The two predominant sources of GABA in the hippocampus are local interneuron firing and projections arising from the basal forebrain (Freund and Antal 1988). Rhythmic firing of GABAergic cells in the basal forebrain, particularly the medial septum, is believed to be critical for the generation of theta activity (Stewart and Fox 1990), and such cells have been shown to preferentially target interneurons in the hippocampus (Freund and Antal 1988). A detailed biophysical model of hippocampal region CA3, incorporating both GABAergic and cholinergic rhythmic input from the medial septum, has recently shown that total $GABA_B$-receptor-mediated conductances in the network does, indeed, rise and fall in rhythm with theta oscillations (Wallenstein and Hasselmo 1997a). In this model, total $GABA_B$-mediated conductance was highest in the early to middle portion of each theta cycle and decayed steadily until the beginning of the next cycle. Here, the beginning of each theta cycle simply corresponded to peaks in pyramidal cell population activity across the entire network (Wallenstein and Hasselmo 1997a).

Considering that such GABAergic modulation may operate in an oscillatory manner with the theta rhythm, it is expected that the relative contributions from afferent (sensory) and intrinsic fibers may also change within each theta cycle. In the present paper we report on a series of simulations that used a recently developed biophysical model of hippocampal region CA3 (Wallenstein and Hasselmo 1997a). It is shown that $GABA_B$-receptor-mediated modulation within a theta cycle enhances the ability of the network

to learn and recall temporal sequence information. This is because afferent information about current location in a sequence dominates early in a theta cycle and gradually activates intrinsic fibers later in the cycle as this modulation is attenuated. During learning, this shift between afferent and intrinsic fiber activation within a theta cycle resulted in the emergence of place fields associated with a given segment of ''locations'' within a larger sequence representing a navigational path. When competition between afferent and intrinsic activity was continual throughout a theta cycle (no GABAergic modulation), place field development was markedly reduced. When GABAergic modulation was included during learning but then removed during a test of recall by positioning the simulated rat at a random location on the previously learned path and tested to see whether the route could be completed, sequence information was not recalled accurately. The result was the recall of a path different from that which was learned. Inclusion of GABAergic suppression of excitatory and inhibitory synaptic transmission at intrinsic fibers during recall enabled an accurate determination of present location because afferent activity dominated early in a theta cycle. This, consequently, fostered the accurate completion of segments of the full sequence during later portions of a theta cycle once intrinsic activity gradually increased. This typically resulted in a completion of the entire path across several theta cycles.

Considering that pyramidal cell excitability is modulated with theta activity (Rudell and Fox 1984; Skaggs et al. 1996), a second focus of the present modeling efforts has been to determine how such modulation may support the systematic phase advance in place cell firing within a theta cycle as a rat passes through the cell's place field (O'Keefe and Recce 1993; Skaggs et al. 1996). Consistent with recent experimental observations (O'Keefe and Recce 1993; Skaggs et al. 1996), we have found *1*) that initial firing as the simulated rat enters the place field of a given cell occurred near or just after the positive peak of the associated theta rhythm; *2*) a systematic advance in firing to earlier phases of the theta rhythm as the rat passed through the place field; *3*) that this phase precession was more dependent on the spatial location of the rat than its velocity through the place field; and *4*) that cells firing early in a theta cycle were typically better predictors of present location than those firing later.

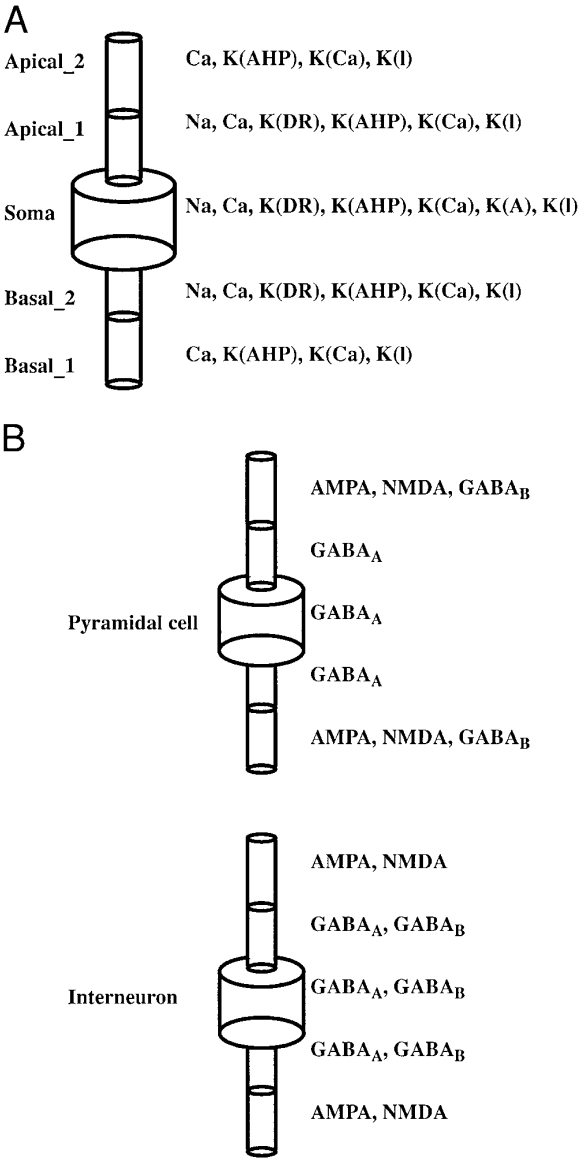

FIG. 1. *A*: spatial distribution of ionic conductances included in the pyramidal cell model (see METHODS for details). *B*: spatial distribution of synaptic currents on each pyramidal cell and interneuron. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid; NMDA, *N*-methyl-D-aspartate; GABA, γ-aminobutyric acid.

METHODS

Computer simulations—single-cell and network biophysics

The model consisted of 1,000 pyramidal cells and 200 inhibitory interneurons. Each pyramidal cell was a reduced five-compartment version of the Traub model (Traub et al. 1989, 1991), which included a fast sodium current, $I_{Na(fast)}$; a delayed rectifier, $I_{K(DR)}$; a high-threshold calcium current, I_{Ca}; two calcium-dependent potassium currents, $I_{K(AHP)}$ and $I_{K(Ca)}$ (Madison et al. 1987); a transient potassium current, $I_{K(A)}$; and a potassium leak current, $I_{K(leak)}$. Each of these currents was located at the soma and proximal dendrites, whereas the distal dendrites contained I_{Ca}, $I_{K(AHP)}$, $I_{K(Ca)}$, and $I_{K(leak)}$ as illustrated in Fig. 1*A*. Calcium buffering was performed in each compartment with the use of a first-order diffusion process (Traub et al. 1991). Each interneuron consisted of $I_{Na(fast)}$ and $I_{K(DR)}$ located at the soma, with the four remaining compartments (2 basal and 2 apical) being passive (see APPENDIX for details).

The principal equation describing the change in pyramidal cell voltage potential in compartment i was given by a discretized version of the cable equation (Rall 1989)

$$C_i\dot{V}_i = g_{i-1,i}(V_{i-1} - V_i) - g_{i,i+1}(V_i - V_{i+1}) - I_{\text{ionic},i} - I_{\text{synaptic},i} \quad (1)$$

where C_i is the input capacitance, $g_{i,j}$ is the conductance between adjacent compartments ($g_{i,j} = 0$ unless $i = j \pm 1$), and $I_{\text{ionic},i}$ and $I_{\text{synaptic},i}$ represent the total intrinsic and synaptic currents in each compartment. Each ionic current was modeled with the use of the Hodgkin-Huxley (1952) formalism, whereas synaptic conductances were expressed as dual exponentials of the form

$$g_{\text{syn}}(t) = \frac{\tau_1\tau_2}{\tau_1 - \tau_2}(e^{-t/\tau_1} - e^{-t/\tau_2}) \quad (2)$$

where τ_1 and τ_2 are the synaptic rise and decay time constants, respectively (APPENDIX). The four synaptic currents included in the model were the chloride-dependent $GABA_A$ and potassium-

dependent $GABA_B$ inhibitory conductances, along with the excitatory α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) conductances.

The synaptic receptor distributions of the pyramidal cell and interneuron types used in the model are shown in Fig. 1*B*. Recurrent excitatory synapses (intrinsic) located at the apical dendrites of pyramidal cells included Hebbian modification of NMDA conductances in conjunction with a voltage-dependent Mg^{2+} block of these channels based on previous modeling (Zador et al. 1990). The network also included recurrent inhibitory synapses ($GABA_A$ and $GABA_B$) at the somata and proximal dendrites of interneurons. Feedforward inhibition of pyramidal cells occurred via $GABA_A$ receptors situated at the somata and proximal dendrites, whereas slower, $GABA_B$-receptor-mediated inhibition was located at distal dendrites (Doi et al. 1990). Feedforward excitation occurred through NMDA and AMPA receptors located at the somata of interneurons. Both cholinergic (Frotscher and Leranth 1985) and GABAergic (Freund and Antal 1988) projections from the medial septum were also included in the model. To maintain consistency with the established distribution of receptor types on each cell and the known effects of cortical modulation from the basal forebrain, cholinergic innervation was represented as a steady-state excitation due to the partial closure of K^+ leakage currents situated at the distal dendrites of both pyramidal cells and interneurons (Madison et al. 1987; Stewart and Fox 1990), whereas GABAergic innervation was expressed as rhythmic IPSPs focused at the somata and proximal dendrites of interneurons (Freund and Antal 1988). Fifteen percent of the total pyramidal cell population and 15% of the total interneuron population were active at any given point in time. All synaptic delays, conduction velocities, and connection probabilities were approximated to parameter estimations made previously from in vivo data (see APPENDIX for details). Connection probabilities were increased in the model in compensation for its reduced scale in terms of cell number compared with slice preparations.

Learning and recall

During the learning period, the network was presented with a sequence of nonorthogonal spatial patterns (average dot product = 0.75). Each pattern can be thought of as a neural representation in the hippocampus (projected from layer II of the entorhinal cortex) of the spatial location of a simulated rat moving along a navigational path. Thus the sequence of nonorthogonal patterns can be thought of as representing a slowly changing route. The rat's velocity during learning was 0.5 m/s (O'Keefe and Recce 1993) unless specified otherwise. For simplicity, we introduced the constraint that one spatial location was normalized to one theta cycle, resulting in a location bin 5 cm in length. The simulated path was 1.5 m long. For purposes of building averages, 50 different sequences (paths) were used in the simulations.

Each spatial pattern was delivered to the model as a fast AMPA-receptor-mediated excitatory (afferent) input to the apical dendrites of pyramidal cells for a period of 20 ms. A different spatial pattern was presented to the network every 100 ms. Thus the entire sequence was delivered to the model as a sequence of spikes riding on the crest of each theta cycle. The entire sequence was repeated five times, constituting the learning period of the task.

At the onset of the learning period, all synaptic weights that scale the NMDA-receptor-mediated conductance in pyramidal cells were initialized to a random distribution. During learning, the synaptic weights were modified with the use of a simple Hebbian-like rule

$$W_{i,j}(t) = W_{i,j}(t-1) + \gamma[\langle v_i \rangle_\tau \cdot \Phi(t)] \quad (3)$$

where

$$\Phi(t) = V_j(t) - V_{\text{threshold}}, \quad \text{when} \quad V_j \geq V_{\text{threshold}} \quad (4)$$

$$\Phi(t) = 0, \quad \text{when} \quad V_j < V_{\text{threshold}} \quad (5)$$

γ is the rate of synaptic modification, $\langle v_i \rangle_\tau$ is the presynaptic firing rate time-averaged across the previous $\tau = 50$ ms, V_j is the postsynaptic voltage potential, and $V_{\text{threshold}} = -30$ mV (Johnston and Wu 1995). Here we have concentrated our efforts toward a biophysically realistic expression for the voltage dependence of NMDA receptor activation (Zador et al. 1990) and have chosen the simplest learning rule possible that is consistent with experimental observations (Kelso et al. 1986; Wigstrom et al. 1986). Note that for potentiation, presynaptic activation must occur before postsynaptic depolarization within a temporal window of τ ms (Larson and Lynch 1989; Larson et al. 1986; Levy and Steward 1983).

During the recall period, the simulated rat was situated at a random location somewhere on a previously learned path with the task of completing the location sequence in the correct order. Information pertaining to the initial position of the rat was expressed as fast AMPA-receptor-mediated EPSPs at the apical dendrites of pyramidal cells coding for the particular location. To maintain consistency with recent experimental observations in vivo, this afferent activity occurred with an $\sim$30° phase delay relative to pyramidal cell population activity being driven by septal influence (O'Keefe and Recce 1993; Skaggs et al. 1996). To probe the ability of the model to complete sequences at different times in a theta cycle, the afferent information was again presented to the model if a second location was not recalled, but with an additional 30° phase delay. This resulted in afferent EPSP-induced firing $\sim$60° phase-delayed relative to septal driving on the next theta cycle. This procedure using 30° increments was repeated within a theta cycle until a second location was recalled. If another location was then not recalled in the span of three theta cycles, the procedure was repeated with the use of afferent information about the current location. Recall performance was quantified with the use of a measure based on normalized dot products between the learned and recalled sequence patterns (Hasselmo et al. 1992). Finally, it should be remarked that no ''rewards'' were given to the rat for successful completion of partial or full segments of the entire location sequence. That is, no use of error or mismatch detection was used in the model.

Quantification of theta and phase between single units and population

Although theta activity recorded from different areas of the hippocampus is generally phase-locked, it is typically not the case that peaks occur at the same point in time (Buszáki et al. 1983; Fox et al. 1986). Thus, to make comparisons with observations from different experiments, we defined phase zero within a theta cycle as the point corresponding to maximal pyramidal cell population activity across the entire network (see Skaggs et al. 1996). The relative phase, ϕ, between theta and single-unit firing was calculated as

$$\phi = 360 \cdot \frac{(\tau_s - \tau_i)}{(\tau_{i+1} - \tau_i)} \quad (6)$$

where τ_s is the time at which a single pyramidal cell fires and τ_i is the time corresponding to the ith peak in pyramidal cell population activity.

RESULTS

Theta and gamma oscillations

When isolated from synaptic influences, each pyramidal cell reproduced several electrophysiological properties known to exist in real CA3 neurons, including the transition from bursting to single-spike firing patterns with increasing levels of somatic current injection (cf. Ranck 1973; Traub

et al. 1991). However, rather than focus on the single-cell level of analysis, our goal in this work has been to understand how modulation, particularly through $GABA_B$-receptor-mediated effects, shapes population behavior. Consequently, we began tests of the model by seeing whether it could reproduce theta and gamma frequency oscillations, two well-known electrophysiological signatures exhibited in in vivo hippocampal recordings (see Bland 1990; Buzsáki 1996). Theta, also known as rhythmic slow activity, is a 4- to 10-Hz field oscillation present in both rodents and primates during exploratory behaviors (O'Keefe and Nadel 1978; Stewart and Fox 1990). This activity is thought to depend in vivo on both rhythmic firing from cells in the medial septum and an intact intrahippocampal network (Ylinen et al. 1995), and can be recorded throughout the entorhinal-hippocampal system. Theta waves are often accompanied by faster gamma oscillations (30–100 Hz), present at the hilus and pyramidal cell layer of CA1 and CA3 (Bragin et al. 1995; Leung 1992). Gamma oscillations have been shown to depend on network interactions of inhibitory interneurons (Whittington et al. 1995) and to be modulated with the phase of the theta rhythm (Bragin et al. 1995).

To see whether theta and gamma oscillations emerge from the elementary biophysical constraints incorporated into the model, we began a simulation by providing a tonic level of excitation to a random sampling of 15% of the pyramidal cells in the network. This was included in the model as a suppression of $I_{K(leak)}$ by reducing the maximum conductance of this current from an initial value of 0.2 nA to 0.02 nA, simulating the slow EPSP recorded in hippocampal pyramidal neurons in vitro under 30 μM carbachol as shown by Madison et al. (1987). This slow EPSP caused a somatic depolarization of ~6.5 mV in pyramidal cells, initiating them into repetitive bursting at slow frequencies in the 0.5- to 2-Hz range. Rhythmic GABAergic input from the medial septum at 10 Hz (Stewart and Fox 1990) produced membrane fluctuations in a random sampling (15%) of interneurons at this theta frequency, with action potentials firing in the gamma frequency range (≈50 Hz) on the depolarized portion of this waveform (Fig. 2*A*). This activity led to summed IPSPs in the tonically depolarized pyramidal cells (through $GABA_A$ synapses), inhibiting them in periodic clusters within the theta frequency range (Fig. 2*B*). The result was a phase difference of ~50° between interneuron and entrained pyramidal cell activity at the theta frequency, consistent with recent in vivo recordings (Fox et al. 1986; Skaggs et al. 1996). When these observations are taken together, they strengthen the view that periodic inhibition of pyramidal cells mediated by summed $GABA_A$ synaptic IPSPs from septally driven interneurons can generate the basic theta rhythm (Buzsáki et al. 1983; Soltész and Deschénes 1993; Ylinen et al. 1995). As is shown in Fig. 2*B*, most pyramidal cells are silent during this simulation. However, because of rhythmic disinhibition they tend to fire

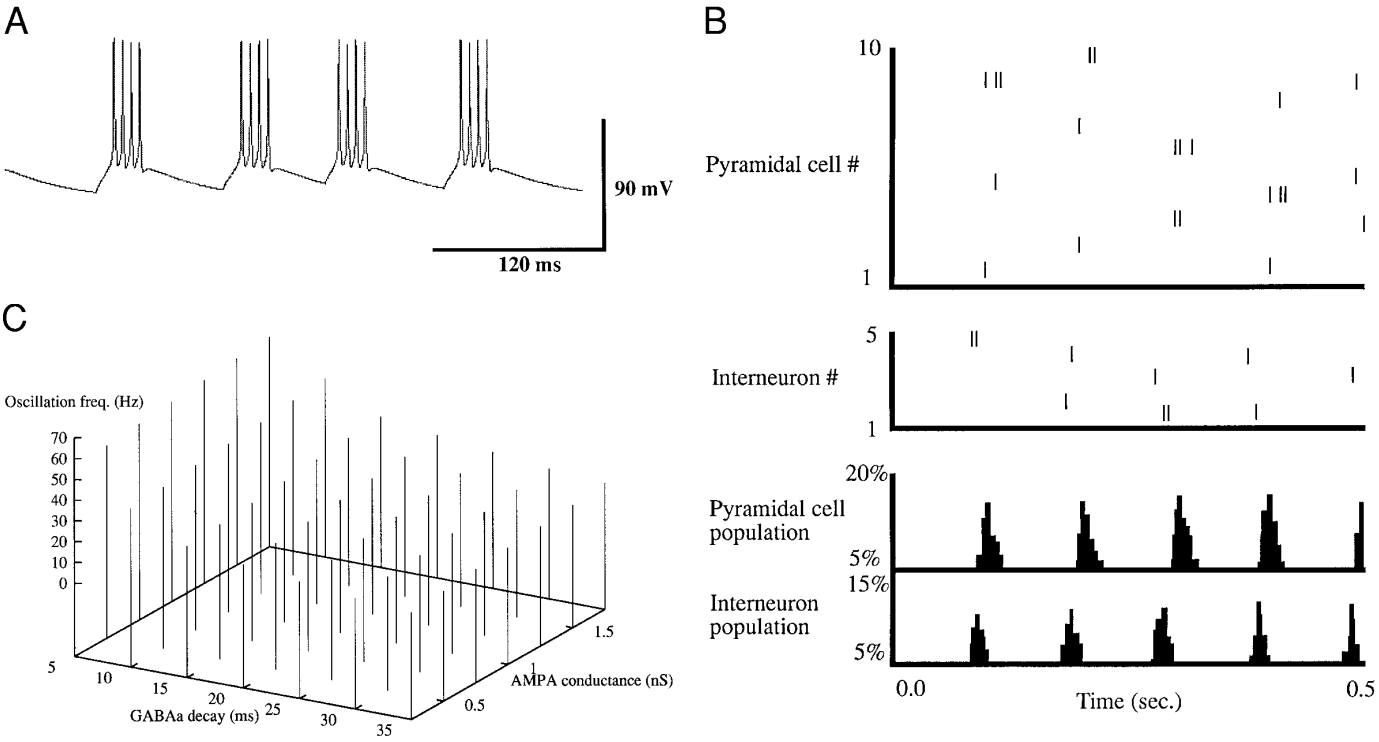

FIG. 2. *A*: representative time series of membrane potential measured at the soma of an interneuron. Note the presence of 2 dominant frequencies at ~10 and 50 Hz. *B*: raster plot of a subset of pyramidal cells and interneurons across 0.5 s of simulation time. Below are the percentage of total population activity for pyramidal cells and interneurons. Note the presence of an ~10-Hz component (theta rhythm) in the population percentages, and a faster (gamma frequency) component in cell firing shown in the raster plots. These data also illustrate the ~60° phase lag of pyramidal cell firing relative to interneuron firing, consistent with recent in vivo hippocampal recordings (Skaggs et al. 1996). *C*: gamma frequency component of interneuron firing was found to vary with both decay constant of the $GABA_A$ synaptic conductance and maximum AMPA synaptic conductance. Fastest oscillation frequency was observed with fast $GABA_A$ decay constants (≈5 ms) and relatively large AMPA conductances (≈1.75 nS).

preferentially with theta resulting in an oscillation of ~10 Hz in peak pyramidal cell population activity, consistent with past experimental observations (Fox and Ranck 1981).

As has been suggested by Buzsáki (1996), gamma oscillations depended on both the intrinsic conductances in interneurons and the time course of their synaptic interactions. The peak frequency of gamma oscillations was found to be increased by either increasing the maximal AMPA synaptic conductance in interneurons or decreasing the decay time constant of the $GABA_A$-mediated Cl^- current in these cells (Fig. 2*C*). The peak gamma frequency was decreased by reversing these operations. This suggests that gamma frequency oscillations may be shaped by both conductances intrinsic to interneurons and the synaptic kinetics governing their interaction. Whittington et al. (1995) recently observed gamma oscillations in a network of interneurons with only inhibitory synaptic connections. They showed that the dominant gamma frequency was dependent on the rate at which $GABA_A$-receptor-mediated conductances decayed (Whittington et al. 1995). Here we show that in addition to the decay time of $GABA_A$ inhibition, the maximum conductance underlying fast excitation (AMPA mediated) may also serve to regulate the fundamental firing frequency in interneurons.

$GABA_B$-receptor-mediated conductances and theta

In this model, the primary excitatory synaptic influence on interneurons was from pyramidal cell activity. Because pyramidal cells tended to fire with theta, converging EPSPs onto an interneuron resulted in interneuron firing in clusters of two to three fast (50 to 80 Hz) action potentials modulated with theta. Rhythmic interneuron firing in clusters at theta frequencies resulted in the initial, rapid increase in $GABA_A$-receptor-mediated Cl^- conductance followed by a slower, long-lasting $GABA_B$-receptor-mediated K^+ conductance in pyramidal cells synaptically coupled to it as shown in Fig. 3*A*. Because interneuron firing typically occurred at theta frequencies and $GABA_B$-receptor-mediated conductances have rise and decay time constants that sum to a period approximately that of a theta cycle (APPENDIX), the total $GABA_B$-receptor-mediated conductances in the network were found to rise and fall in a rhythmic manner with theta oscillations as illustrated in Fig. 3*B*.

This has interesting consequences for the activity levels of single units within a theta cycle. There are primarily three effects of $GABA_B$ receptor activation on pyramidal cells of concern here: *1*) the suppression of excitatory synaptic transmission at recurrent collaterals among pyramidal cells (Ault and Nadler 1982; Colbert and Levy 1992); *2*) the suppression of inhibitory synaptic transmission at pyramidal cells and interneurons (Davies et al. 1990; Howe et al. 1987); and *3*) the direct postsynaptic inhibitory potential (IPSP) resulting from a slow but long-lasting influx of K^+ ions into the cell (Newberry and Nicoll 1984). The combined result of these three effects in our model was a net reduction in the excitatory activity of pyramidal cells at portions of each theta cycle where $GABA_B$-receptor-mediated conductances were highest (Fig. 3*A*). The first effect limited EPSPs in pyramidal cells from other pyramidal cells, whereas the second and third effects modulated IPSPs to pyramidal cells from inhibitory interneurons. Taken together, these effects resulted in an overall increase in the number of pyramidal cells firing in the network once $GABA_B$-receptor-mediated conductances began to decline. This increase in population activity typically lasted between 30 and 60 ms and was initially weakened by fast $GABA_A$-receptor-mediated IPSPs through disynaptic activation of interneurons as shown in Fig. 2*B*. This finding that pyramidal cells displayed a tendency to fire at a specific phase of an ongoing theta rhythm is consistent with recent in vivo hippocampal recordings from rodents (Fox et al. 1986; Skaggs et al. 1996).

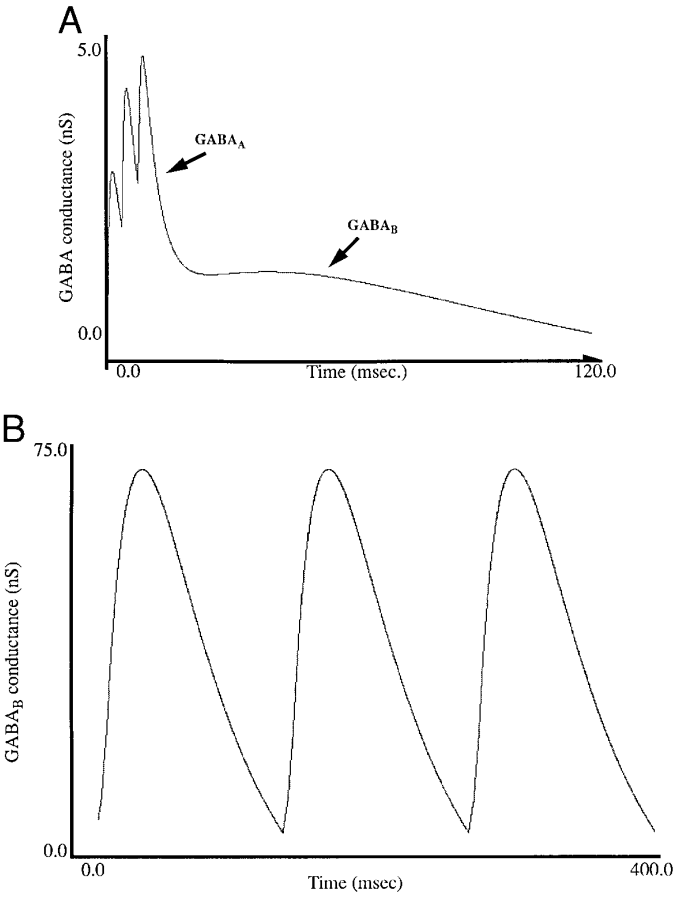

FIG. 3. *A*: GABA-receptor-mediated conductance measured in a single pyramidal cell across a theta cycle. The 3 fast peaks are due to activation of $GABA_A$ receptor channels (by a series of 3 action potentials from a presynaptic cell), which contribute to a Cl^--supported inhibitory postsynaptic potential (IPSP). Later peak is due to activation of $GABA_B$ receptor channels, which contribute toward a slow-onset, but long-lasting, IPSP mediated by K^+ ions. *B*: total $GABA_B$-receptor-mediated conductance in the network rises and falls in an oscillatory manner with the accompanying theta rhythm. Here the conductance is shown across 3 consecutive theta cycles.

Learning sequence information and the development of place fields

A completion task was employed to determine whether the model was capable of learning and recalling temporal sequence information. A sample input sequence is shown in Fig. 4*A*. Note the presence of random background firing of pyramidal cells (15% of total pyramidal cell population at

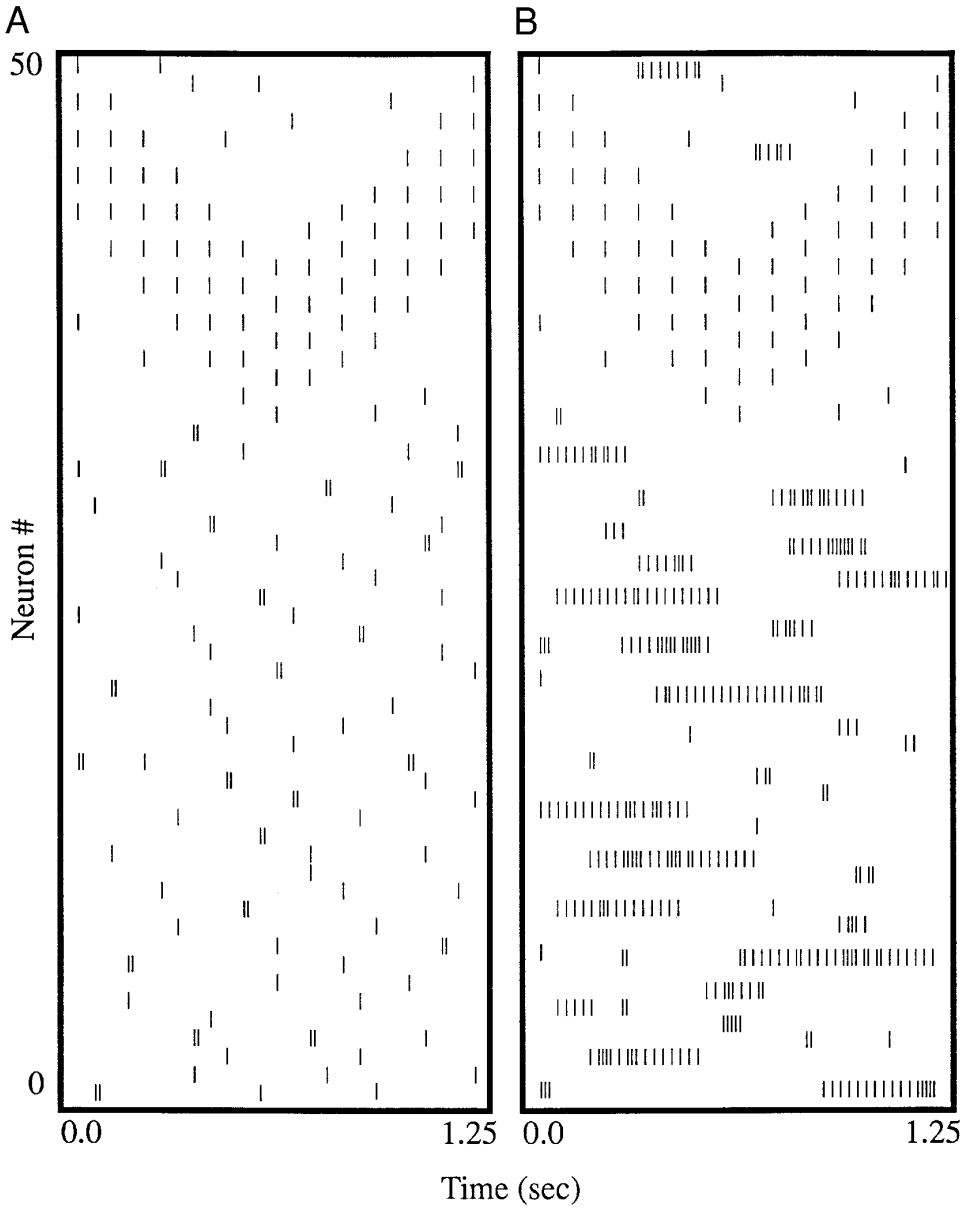

FIG. 4. Activity of a subset of 50 pyramidal cells (from a total of 1,000) in the model in response to a sample input sequence (*A*) before learning and (*B*) on the fourth learning trial. Initially, background activity (15% of the total pyramidal cell population) appears randomly—different cells fire at different times. After several learning trials, however, this activity becomes more persistent. Some cells begin to fire in a sustained fashion over contiguous segments of the input sequence. This sustained firing resembles the formation of place fields observed in hippocampal in vivo recordings (McNaughton et al. 1983; O'Keefe and Dostrovsky 1971).

any given point in time) unrelated to the input sequence. This activity is due to a cholinergic depolarization of pyramidal cells (mediated by a suppression of K^+ leakage currents) (Madison et al. 1987) from septal sources (see METHODS for details) and, as will be shown below, provides a necessary ingredient for the successful learning and recall of sequence information and the development of place fields during learning. During the learning period, it became apparent that many of the cells that fired independently of the input pattern for a brief period of time (i.e., during a single pattern in the sequence) in the initial stages of learning began to fire continuously over a portion of the full sequence pattern after several exposures. Thus, with repeated exposure to the full sequence, these cells learned to respond to particular subsequences as shown in Fig. 4*B*. Considering that a pattern in the sequence can be thought of as representing a specific spatial location of a rat in a learning environment and the full sequence as the rat's path in that context, the behavior of the cells that fired over a contiguous portion of the full sequence is analogous to the development of place fields (McNaughton et al. 1983; O'Keefe and Dostrovsky 1971). Indeed, a visual inspection of Fig. 4*B* indicates that the entire sequence, which represents the rat's full path, is reconstructable from the appropriate interdigitation of these cells representing particular subsequences (place fields). This finding is similar to that observed in a computational model by Levy (1989, 1996), who showed that ''context-dependent'' cells may emerge during learning in sparsely connected recurrent networks under restricted levels of activity with the use of a mismatch detecting scheme. Here we show that such cells arise naturally in a biophysically realistic model of region CA3 without the need for additional rules concerning match detection.

In the present model, place cells begin to develop when *1*) a sufficient number of ''background'' cells fires during learning to ensure that some connection exists to cells in the input

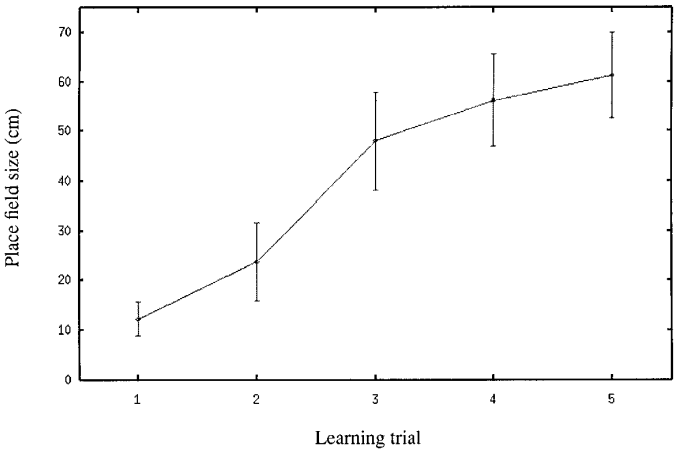

FIG. 5. Average (across suitable background cells—see text for details) place field size was measured after each learning exposure to the full input sequence. Both size of place fields and the observation that size increased with learning have been observed in recent hippocampal in vivo recordings (Mehta and McNaughton 1997; O'Keefe and Recce 1993).

sequence; and *2*) when cells related to the input sequence fire before background cell depolarization, but within the time span appropriate for LTP (~50 ms). This gradually strengthens the connection between sequence- and background-related cells for one pattern in the sequence. During learning, if the next pattern in the sequence occurs closely in time following activity in these background cells, new associations will be made between the background cells and those cells related to the next pattern in the sequence. This process is, of course, dependent on cells related to the latter sequence pattern firing closely enough in time after background activity associated with the previous sequence. However, because these connections are asymmetric, this potentiation can serve in the development of place fields even if it occurs at a much later time during the learning period. Indeed, the likelihood of the secondary potentiation increases with repeated exposure to the full sequence because background cell firing preferentially occurs near zero phase in the theta rhythm while the presentation of the sequence is essentially random with respect to the phase of this reference. Thus, in addition to serving as a basis for the development of place fields during learning, this mechanism also indirectly allows for the time spanning association of distinct events across an interval greater than that of normal NMDA-receptor-dependent LTP (Larson and Lynch 1989; Levy and Steward 1983).

To make estimates of place field size and development during learning, we let the velocity of the simulated rat equal 0.5 m/s, which is consistent with recent observations by O'Keefe and Recce (1993). For simplicity, we have introduced the constraint that one spatial location along the simulated path is normalized to one theta cycle during learning, resulting in a location bin 5 cm in length (METHODS). This allowed us to estimate the size of place fields at different stages of learning. The size of a place field was calculated when a background cell exhibited sustained firing during the presentation of two or more contiguous patterns in a given sequence. Figure 5 shows the average place field size following each learning exposure to the same sequence of locations within a given trial. Across the entire network, the average place field size was 23.8 cm after the second exposure and systematically increased to a size of 61.3 cm after the final exposure. The growth rate of a place field was found to be most sensitive to the rate of synaptic modification (γ in *Eq. 3*) and the maximum conductance underlying AMPA and NMDA postsynaptic potentials in pyramidal cells. This range of place field sizes is consistent with recent in vivo experiments (O'Keefe and Recce 1993), as is the observation that place field size increased with learning (Mehta and McNaughton 1997). Furthermore, because the overlap between place fields also increased with learning, the temporally asymmetric potentiation between place cells associated with spatially contiguous fields resulted in earlier firing of a cell as the rat entered the cell's place field after repeated exposures. This translated into a general broadening of place field size with learning (as shown in Fig. 5) in the direction opposite to that traversed by the rat. This result has in fact been observed in recent in vivo hippocampal recordings from rodents (Mehta and McNaughton 1997).

Recalling sequence information and the phase precession effect

Sequence recall was tested by placing the simulated rat at a random location on a previously learned path and determining whether the remaining sequence (navigational route) was completed. To remain consistent with recent experimental observations in vivo, this initial afferent activity occurred with an ~30° phase delay relative to pyramidal cell population activity being driven by septal influence (O'Keefe and Recce 1993; Skaggs et al. 1996). If the sequence was not completed, the initial afferent pattern was again presented to the model, but with an additional 30° phase delay relative to peak pyramidal cell population activity. In this manner, the model was probed for sequence completion at different phases of a theta cycle (see METHODS for details). Figure 6 shows an example of the cellular activity accompanying this task, in which the sequence to be learned is presented at *top left*. In this example, the initial pattern was presented to the model at four different phases of a theta cycle. The remaining segment of the sequence was not completed in response to probes presented early in the theta cycle, but was completed when this information was presented later. This is because network $GABA_B$-receptor-mediated conductances (Fig. 6, *bottom*) and the subsequent suppression of excitatory synaptic transmission were relatively high during the early phase of each theta cycle and consequently intercellular spread of activity among pyramidal cells was minimal. As $GABA_B$-receptor-mediated suppression of EPSPs at recurrent collaterals of pyramidal cells was reduced later in each theta cycle, more of the full sequence was recalled (Fig. 6). Because cellular activity from both afferent and intrinsic (recurrent) fibers competed later in each theta cycle, cells that fired early in a cycle were typically better predictors of location within a sequence than those firing later. This result is consistent with recent hippocampal recordings from place cells in region CA1 (Skaggs et al. 1996).

Because $GABA_B$-receptor-mediated effects modulated pyramidal cell firing with the theta rhythm, cells directly related to the sequence pattern as well as those exhibiting place cell

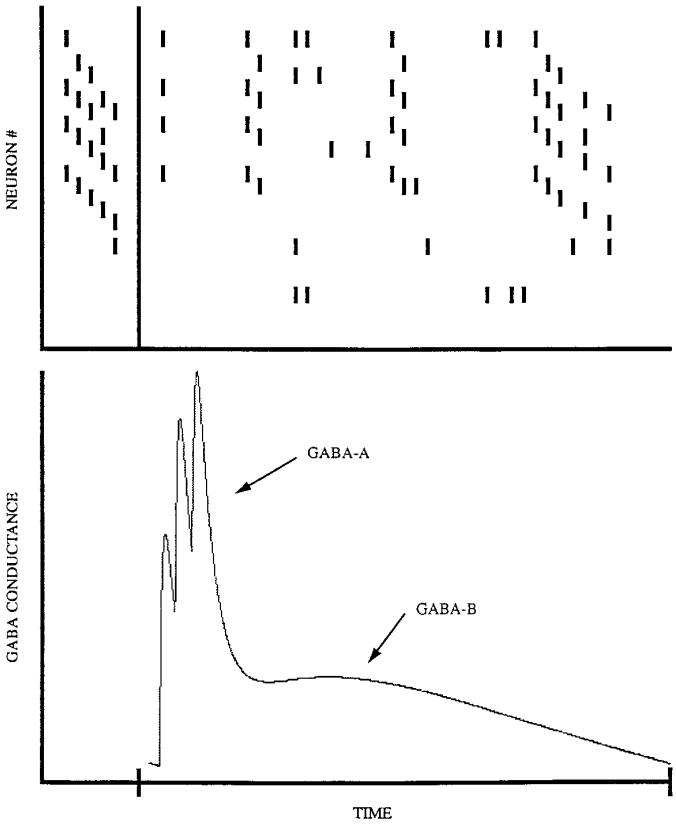

FIG. 6. Probing for recall. *Top*: model learned a sequence of 5 spatial patterns (shown at *far left*). To test recall, the 1st input pattern of the sequence was presented to the model at different times in a theta cycle to probe for accurate completion of the full sequence. When network $GABA_B$-receptor-mediated conductances (*bottom*) and subsequent suppression of excitatory postsynaptic potentials (EPSPs) and IPSPs was high during early portions of the theta cycle, only the 2nd pattern was recalled in response to the initial pattern. However, when GABAergic modulation decayed toward the end of the theta cycle, the full sequence was completed in response to the initial input pattern.

behavior tended to preferentially fire toward the latter portion of each theta cycle. The initial cell firing as the rat was situated at a random location on a previously learned path was always dominated by afferent activity related to the present location, because intrinsic fibers at recurrent collaterals were suppressed early in each theta cycle. Information about future locations became available later in each cycle once this suppression was attenuated. At the start of the next theta cycle, the present location of the rat was again updated by a dominant afferent activity pattern and the scenario was repeated. This typically resulted in a place cell firing late in a theta cycle as the rat initially entered that cell's field. Several locations were then rapidly recalled late in a theta cycle with sustained place cell firing across a contiguous segment of locations. As the rat exited a place field, activity of the associated place cell was then usually shunted during the early portion of the next theta cycle because of $GABA_B$-receptor-mediated suppression of EPSPs at recurrent collaterals. Thus the phase of the theta cycle at which a place cell fired systematically advanced as the rat passed through the cell's place field. This is illustrated in Fig. 7*A* (compare with experimental results shown in Fig. 7*B*), which shows the activity of a single place cell plotted as a function of the phase in the theta cycle and spatial location of the rat when it fired.

The observations that as a rat enters a place field, activity in the associated cell typically begins at the same point in a theta cycle, and advances toward earlier phases as the rat exits the field, are both supported by recent in vivo hippocampal recordings (O'Keefe and Recce 1993; Skaggs et al. 1996).

To determine whether the phase advance of place cell firing was more dependent on the spatial location of the rat or the amount of time spent in a given place field, a series of simulations was carried out with the use of different values for the average velocity of the rat during learning as it passed through the field. As illustrated in Fig. 8, the slope of the average phase

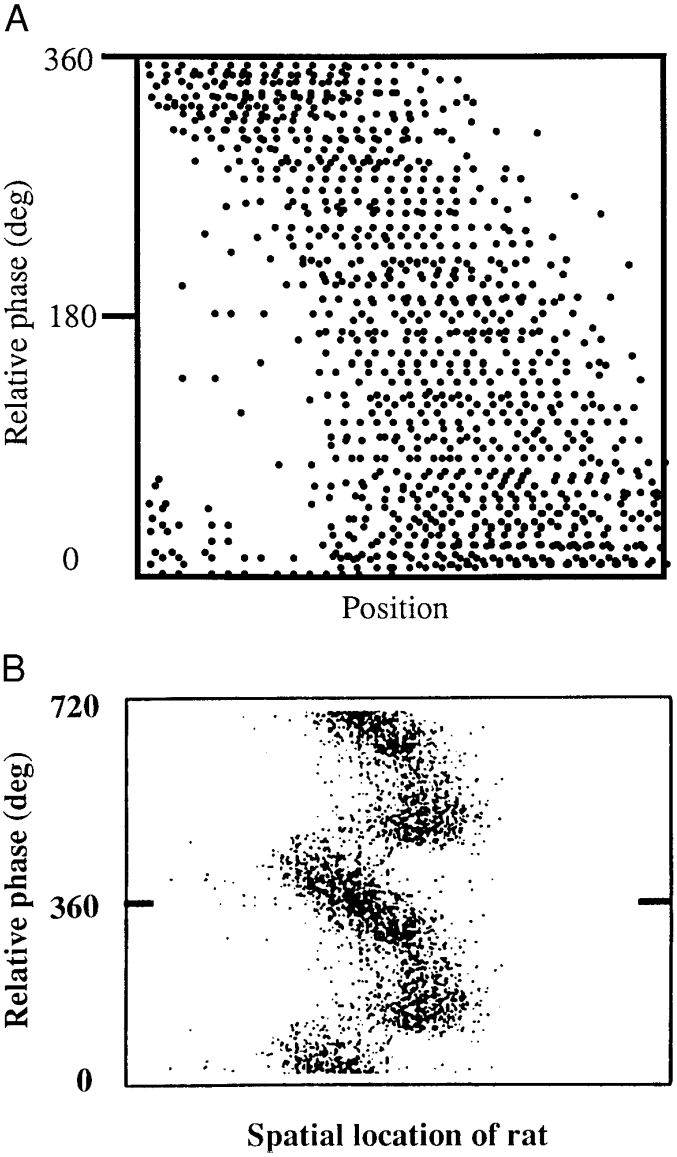

FIG. 7. Phase precession. *A*: representative firing pattern from a single place cell as the simulated rat passed through the place field of the cell. Note systematic advance from firing late in a theta cycle when the rat first entered the field, to firing earlier in the cycle as the field is exited. *B*: this effect has recently been observed in hippocampal in vivo recordings (O'Keefe and Recce 1993; Skaggs et al. 1996). (Figure adopted from Skaggs et al. 1996 with permission.)

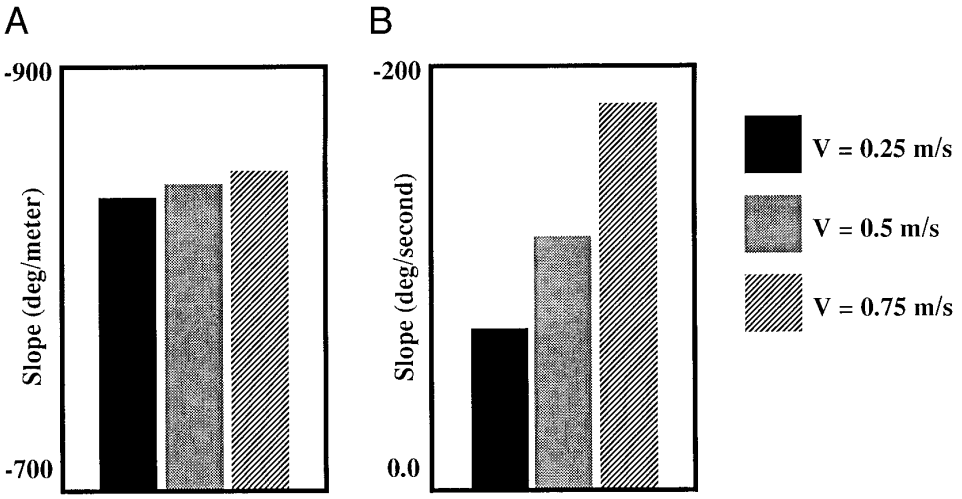

FIG. 8. Average slope of phase precession of place cell firing corresponded better with (*A*) position of rat in the field than (*B*) time spent in the field. Here, 3 different rat velocities (V) were used in the simulations, and they show that a different degree of phase precession occurred with time depending on the velocity of the rat. However, degree of phase precession with position was virtually unaffected by different velocities. This result is consistent with recent experimental recordings (O'Keefe and Recce 1993; Skaggs et al. 1996).

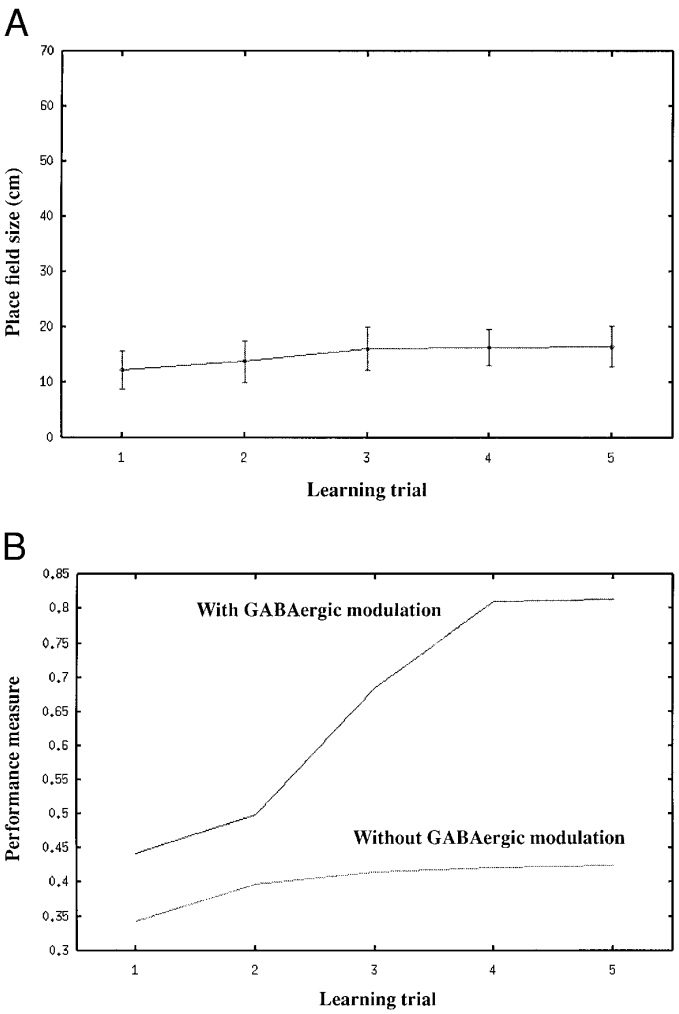

FIG. 9. *A*: average place field size was measured after each learning exposure to the full input sequence. When compared with Fig. 5, simulations without GABAergic modulation exhibited substantially reduced place field development. *B*: average recall performance (see METHODS for details) of the model after each learning trial with and without GABAergic modulation. Here, GABAergic modulation allows the model to complete sequence information more accurately compared with when such modulation is not incorporated in the network.

(across 50 runs with the use of a linear regression) of place cell firing was more sensitive to time than to spatial location. That is, different rat running speeds produced different phase relationships. However, the phase relationships were all approximately the same when plotted against spatial location. This is because although the $GABA_B$-receptor-mediated suppression of EPSPs and IPSPs supporting this effect operated in a periodic manner with the theta cycle, the development of place cell firing patterns depended primarily on when information was obtained about present location. This information typically dominated early in a theta cycle and competed at later portions of a cycle with information pertaining to future locations once the present locale was determined. Thus the firing pattern of a place cell during recall directly depended on the ability of the model to accurately determine the current location of the rat before proceeding. This information was indirectly modulated in the model by the relative contributions of afferent (sensory) and intrinsic (recurrent) fibers during a theta cycle. Consequently, a rat could conceivably remain at a given location for a period of time with no change in place cell firing until the next location was determined. The observation that the phase precession of place cell firing is more dependent on spatial location than on time in the cell's place field is consistent with recent in vivo hippocampal recordings by O'Keefe and Recce (1993).

$GABA_B$-receptor-mediated suppression of EPSPs and IPSPs is critical for the development of place fields and the phase precession effect

The same simulations described above were also carried out without the $GABA_B$-receptor-mediated suppression of EPSPs and IPSPs included in the model to determine how this modulation influenced place field development and the phase precession effect. The net effect of these two processes was a decrease in pyramidal cell excitability (intrinsic fibers) during early portions of each theta cycle. Without this suppression during learning, place field development was attenuated as indicated in Fig. 9*A*. This is because during the early portion of each theta cycle afferent information about present location now competed with information from all previously learned locations. This resulted in a decrease in the ability of the model to accurately determine the present location and also resulted in frequent errors in sequence

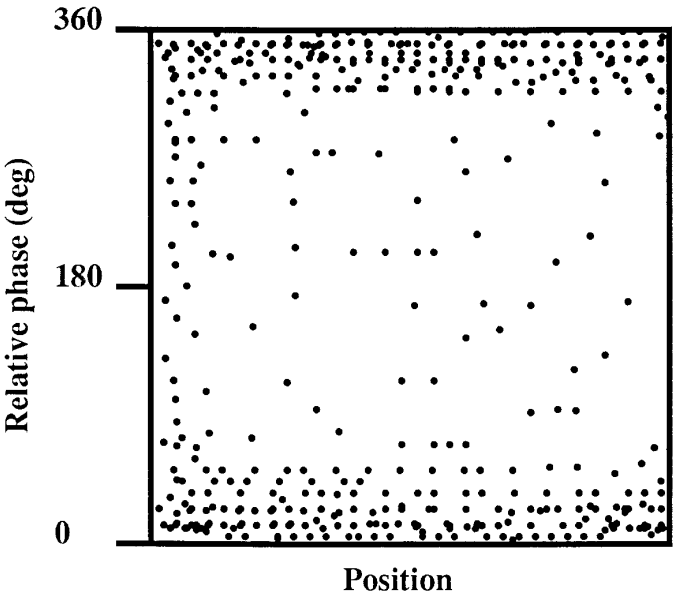

FIG. 10. Representative firing pattern from a single place cell as simulated rat ran through the place field of the cell demonstrates that without GABAergic modulation, firing tended to cluster around 0 phase of each theta cycle. This was due to a marked reduction in place field development without GABAergic modulation and increased competition between afferent and intrinsic activity during early portions of each theta cycle, when afferent sources typically dominated with GABAergic modulation included in the model (Fig. 7).

order. Thus place field development in this model was dependent on an unambiguous estimate of present location in a given sequence as well as a gradual introduction of pyramidal cell activity at intrinsic fibers rather than a consistently uniform (across an entire theta cycle) level of competition among cells coding for different locations.

Because place field development was curtailed without GABAergic modulation, recall of sequence information was equally problematic. First, the same difficulty in determining the present location that hindered place field development during learning also made recall difficult because locations previously stored during learning were now as active as afferent information about present location throughout the entire theta cycle. However, even when the present location was accurately determined, sequence information was not preserved because of discontinuities in place field development. This frequently resulted in inaccuracies in sequence recall as illustrated in Fig. 9*B*, which shows recall performance (see METHODS for details) of the model after each learning trial, with and without GABAergic modulation. Both learning and recall of sequence information benefited from GABAergic modulation by having *1*) a portion of a theta cycle where afferent information about present location dominated and was determined unambiguously and *2*) a gradual increase in excitability of pyramidal cells related to previously stored locations in the sequence once the present location was determined. This gradual increase in activity at intrinsic fibers allowed a small subset of previously learned locations to compete, rather than the entire set, and minimized the likelihood of errors in sequence order. Both of these components were necessary for place field development and the subsequent preservation of sequence information in this model.

Because place field formation was attenuated without GABAergic modulation, background cell firing, which was the source of place field development, appeared to remain clustered near zero phase of each theta cycle, corresponding to maximum pyramidal population activity. Thus this activity was largely independent of the present location of the simulated rat. Consequently, as demonstrated in Fig. 10, no phase advance (as compared with Fig. 7) was present as a function of the spatial location of the rat when GABAergic modulation was not included in the model. This is primarily attributable to discontinuities in place cell firing as indicated above and in Fig. 9*A*.

DISCUSSION

$GABA_B$ receptor activation and sequence learning

The two predominant sources of neuromodulation from the medial septum to the hippocampus are cholinergic and GABAergic. Considering that the cholinergic effects on pyramidal cell activity are believed to develop slowly (Dutar et al. 1995), and operate on a time scale greater than a theta cycle, it is unlikely that such modulation shapes population activity in a periodic manner. GABAergic modulation, on the other hand, may indeed influence hippocampal pyramidal cell activity on a time scale consistent with the theta rhythm. This is because in addition to the rhythmic septal influence, CA3 interneuron firing time-locked to theta oscillations (Ylinen et al. 1995) provides a local source of GABA, and the time constants governing the synaptic kinetics for both $GABA_A$ and $GABA_B$ receptor activation fall within the approximate period of a typical theta cycle. Considering this, we have used a detailed biophysical model to investigate how periodic modulation by $GABA_B$ receptor activation affects population behavior in region CA3. In our model, this rhythmic change in network $GABA_B$-receptor-mediated conductance levels was dynamically created because of the interplay of septal driving and intrinsic synaptic kinetics. However, verification of such rhythmic behavior in the hippocampus still awaits experimental observation. An initial test of this could entail stimulating the septum at a frequency slow enough that changing levels of hippocampal GABA are reflected by in vivo microdialysis methods. Moreover, a detailed knowledge of the time scales involved in GABAergic modulation of synaptic transmission must be obtained. In the model, we began by noting that $GABA_B$ receptor activation has three effects of interest at the cellular level of observation: the suppression of both excitatory and inhibitory synaptic transmission at intrinsic fibers and a direct IPSP. The organization of these cellular effects has interesting consequences for population behavior as observed in our network model. Their net effect is a decrease in pyramidal cell excitability at intrinsic (recurrent) fibers relative to afferent (sensory) innervation during early portions of a theta cycle when $GABA_B$-receptor-activation is highest, and a gradual increase in intrinsic activity as this activation level decays toward the third quarter of a theta cycle. This periodic change in the relative contributions of afferent and intrinsic information to population dynamics was found to be critical for the development of place fields and subsequent learning and recall of sequence information.

As shown in Figs. 5 and 9, place field development criti-

cally depended on an unambiguous determination of the present location within a sequence. When intrinsic fibers were active early in the theta cycle (without GABAergic modulation), they competed with afferent information coding for location, which led to occasional errors in sequence completion (Fig. 9). Furthermore, such competition, when continuous across an entire theta cycle, hindered the subsequent development of place fields even when the present location was accurately determined, because the full set of sequence locations was available at each time step. When GABAergic modulation was included in the model, however, the afferent pattern that dominated early in the cycle was associated initially with only a reduced subset of proximal sequence locations because the suppression of EPSPs and IPSPs at intrinsic fibers declined in a graded manner in proportion to $GABA_B$ receptor activation. This suggests that selective $GABA_B$ receptor antagonists such as phaclofen and 3-amino-propyl-*n*-butyl-phosphinic acid (CGP 36742) should attenuate the development of place fields in vivo and reduce an animal's capacity for sequence learning. Moreover, because $GABA_B$ receptor activation suppressed EPSPs at intrinsic fibers early in a theta cycle, we found preferential firing of pyramidal cell activity toward the end portion of each cycle. This tendency for pyramidal cells to fire at a specific phase of a theta cycle has been observed in hippocampal in vivo recordings (Fox et al. 1986; Skaggs et al. 1996). Thus $GABA_B$ receptor antagonism should partially reduce this tendency for firing at a particular phase of a theta cycle and result in a broader distribution of activity over time.

These observations demonstrate that place fields can, in theory, develop without a preexisting attractor structure before learning (O'Keefe and Nadel 1978). However, at present it is still an open question as to whether or not this occurs in the same manner in the hippocampus. There is some evidence for hippocampal place-specific firing in rats introduced to an environment in total darkness (Quirk et al. 1990). However, in this study, once the environment was illuminated the fields gradually came under the control and rotated with input from visual cues (Quirk et al. 1990). Thus it is still an unresolved issue as to how much place field development depends on visual stimuli versus an animal's previous experience in different learning environments.

The neural mechanism presented here also shows that organization of place fields from initially random, background activity can serve as context information for relational memory in general. That is, the mechanism provides a resolution to the problem of associating or ''binding'' temporally distinct events where the period separating them is greater than the time window normally associated with LTP of a synapse (typically ~50 ms or less) (Larson and Lynch 1989; Larson et al. 1986; Levy and Steward 1983). Thus time-dependent information can be learned and serial ordering preserved accurately even when the period between individual patterns in the sequence is an order of magnitude greater than that normally associated with LTP of a single synapse (e.g., Fig. 4*B*).

$GABA_B$ receptor activation and phase precession

The generating mechanisms and functional properties of hippocampal theta oscillations are not completely understood at present. It appears from both electrophysiological experiments (Lee et al. 1994; Stewart and Fox 1990; Ylinen et al. 1995) and computational models (Traub et al. 1989; Wallenstein and Hasselmo 1996, 1997b) that tonically activated pyramidal cells in conjunction with rhythmic driving of interneurons from the medial septum can support periodic, extracellularly recorded field oscillations in the theta frequency range. These studies have attempted to understand the basis for theta rhythmicity by examining the relationship between the field oscillation, single-cell behavior, and the synaptic kinetics governing population activity. It has been observed that most pyramidal cells are silent in the CA1 and CA3 regions during exploratory behavior, when theta activity dominates (Buzsáki et al. 1983). The pyramidal cells that are active typically only fire when the animal enters the ''place'' field associated with that cell. Some questions that arise from these observations include the following. *1*) How is theta activity related to the information carried in place cell firing? *2*) Given that place learning is a temporal as well as spatial phenomenon, how is sequence information preserved in place cell firing patterns?

The discovery by O'Keefe and Recce (1993) that place cell firing systematically advances to earlier phases of each theta cycle as a rat runs through the associated place field of that cell provides a starting point to answer both of these questions. It is now clear that in addition to firing rate, place cell activity contains information regarding the temporal dynamics of an organism's navigational route. An ambiguity exists in determining the specific location within a place field by using firing rates alone. However, both the entrance and exit from a place field can be determined by the phase of the spikes alone. Moreover, considering that place cell firing advances relative to theta activity with movement through the field, one can envision a ''chaining'' together of successive fields that preserves sequence information based on phase. Partial overlap of place fields could be disambiguated because cellular activity associated with the field being entered should have a greater phase delay than that associated with the field being exited relative to the local theta oscillation. Thus the amount of phase delay proceeds in the direction of movement.

In our model, place-specific firing arose from random background activity that initially was unrelated to any particular location in the sequence. However, with learning, some of these cells began to fire in a sustained manner across a contiguous segment of locations in a sequence. The firing of these place cells was found to phase advance with movement through the associated place field. This phase advance occurred because as the simulated rat entered a new location, activity associated with the upcoming field occurred late in a theta cycle as GABAergic suppression of intrinsic fiber activity related to future locations declined. This resulted in place cell activity related to the next place field initially firing toward the end of a theta cycle. As the rat moved into the field, EPSPs from afferent sources containing information about the current location also contributed to the place cell's firing activity. Because this afferent activity typically dominated early in a theta cycle, the cell associated with the present place field now began to fire at an earlier phase, whereas place cells associated with the next location in the sequence began to fire later in that cycle. This scenario re-

sulted in a full sequence being recalled on the basis of the temporal interdigitation of individual place cell firing patterns (Figs. 6 and 7).

This mechanism for phase precession can be tested experimentally. The model predicts that selective $GABA_B$ receptor antagonists such as phaclofen and the orally active CGP 36742 should reduce the phase precession effect (assuming place fields have developed normally) by making it just as likely for place cell firing to be observed associated with future locations (intrinsic sources) at early portions of a theta cycle as it is during later portions. This would not completely inhibit phase precession, but would smear it in that the distribution of firing activity would show increased variability as the organism enters the place field of the associated cell. Furthermore, any events that block or delay afferent sources impinging on place cells along the perforant path such as lesions or cooling should inhibit the advance of place cell firing toward earlier phases of a theta cycle.

Comparison with other models

The purpose of this model is *1*) to show that sequence learning and recall are possible in a network model without relying on physiologically unrealistic mechanisms; *2*) to elucidate the role of $GABA_B$ receptor activation in setting the appropriate dynamics between afferent and intrinsic sources of information during learning and subsequent place field development; *3*) to understand how this same mechanism may also support the phase precession effect during recall; and *4*) to relate cellular effects (e.g., $GABA_B$ suppression of EPSPs and IPSPs) to population events (theta and gamma oscillations—phase precession of place cell firing relative to theta) and ultimately behavior (sequence learning and recall). To this end, the model has explored how several specific phenomena can be accounted for in a biophysically realistic manner. The modeling has also demonstrated the importance of examining several levels of observation simultaneously, a practice that is often not feasible in an experimental setting.

There are several features of our model that merit comparison with those used by other investigators to understand phase precession and place field development. For instance, two recent models of phase precession have also found the ratio of the strengths of external to internal connections to be a critical factor in accounting for this phenomenon, but neither model demonstrated a specific physiological mechanism for its modulation (Jensen and Lisman 1996; Tsodyks et al. 1996). We started with a model that resulted in phasic modulation via the selective $GABA_B$-receptor-mediated suppression of EPSPs and IPSPs at intrinsic (recurrent) fibers while leaving afferent innervation dominant early in each theta cycle. Thus the necessary phasic modulation emerged from elementary biophysical constraints at the cellular level of observation. Consequently, we found that such modulation should not be considered a static variable, but must be dealt with on the basis of the synaptic kinetics contributing to its phasic appearance.

In our model, the phase precession effect occurred primarily due to $GABA_B$-receptor-mediated suppression of EPSPs at intrinsic fibers early in each theta cycle. This modulation reduced the spread of activation to other locations in the sequence. Consequently, when the simulated rat entered a new location, initial activation (stemming from the previous location) typically started late in a theta cycle and advanced as the rat passed through the location. Once the current location was entered, afferent activity associated with it dominated during the early portion of the next theta cycle. Thus sequences were recalled rapidly, but different lengths of sequences were obtained during different components of theta. This mechanism stands in contrast to models that obtain precession due to the slow recall of sequences across theta cycles, including *1*) a model that depends on the use of much weaker excitatory connections with asymmetric synaptic weights (Tsodyks et al. 1996) and *2*) a model that depends on the slow time course of NMDA-receptor-mediated conductances during recall (Jensen and Lisman 1996). This mechanism also stands in contrast to models that use weakly detuned coupled oscillators to account for the phase advance (O'Keefe and Recce 1993).

We have also attempted to realistically model the development of place fields and how they change over time. Any model that seeks to show a common mechanism relating place field development and the phase precession effect must be able to account for basic experimental data on place field genesis and change with learning. Thus models of these phenomena in which place cells are ''labeled'' in a predetermined manner are problematic in that place fields are assumed to exist from the beginning rather than being formed through a learning process (e.g., Tsodyks et al. 1996). This is further complicated if the synaptic strengths and the sizes of place fields in the model are also predetermined, allowing no assessment of how place fields form or how they may change with learning (e.g., Tsodyks et al. 1996). In our model, place fields emerged gradually from spatially random background activity (Fig. 4, *A* and *B*) given that certain conditions are satisfied with respect to the connection probabilities of these cells with cells belonging to the sequence pattern and the relative timing of this activity with that being driven from afferent sources (see RESULTS). In this regard, our model has commonalities with work by Levy and colleagues (Levy 1989, 1996). Our model also has similarities with those that emphasize the development of asymmetric synaptic connections, critical for place field development and sequence learning (Blum and Abbott 1996; Kleinfeld and Sompolinsky 1988; Levy 1996).

We also show in our model how realistic constraints at the cellular level result in an accurate account of population behavior such as observing theta and gamma oscillations. This is additionally important when one considers that models of phase precession must depend on timing characteristics consistent with these experimental signatures. Thus models that rely on encoding 7 ± 2 memories stored across seven gamma cycles evenly distributed within each theta cycle (e.g., Jensen and Lisman 1996) fail to account for the observation that pyramidal cells in the hippocampus have been shown to fire at preferred phases of the theta rhythm (Rudell and Fox 1984; Skaggs et al. 1996). Moreover, such an encoding scheme results in an essentially discontinuous learning process. In our model, preferential firing of pyramidal cells at a particular phase of the theta rhythm was the result of both phasic input from the medial septum and both pre-

and postsynaptic suppression of pyramidal cell activity mediated by $GABA_B$ receptor activation.

LTP and phase precession

The $GABA_B$ agonist baclofen has been shown to facilitate LTP in the hippocampus (Burgard and Sarvey 1991). Mott and Lewis (1991) found that 5-Hz stimulation of a hippocampal slice led to a reduction in $GABA_A$ inhibition and a subsequent increase in NMDA-receptor-mediated excitation and finally LTP induction. This process was prevented with application of the $GABA_B$ antagonist saclofen. Thus $GABA_B$-mediated suppression of inhibition seems necessary for the induction of LTP in hippocampal slices. Similar observations have been made with higher-frequency stimulation where inhibition decreased due to action at a $GABA_B$ autoreceptor (Davies et al. 1990). Considering that $GABA_B$-receptor-mediated conductances were found to rise and fall with theta oscillations in this model, this raises the possibility that LTP induction may occur at preferential phases of the theta rhythm. Pavlides et al. (1988) have in fact shown that stimulation of the perforant path during the peak in dentate theta produced LTP, whereas stimulation at the trough produced a decrease in synaptic efficacy or no change at all.

The observation that initial cell firing as an organism enters a place field is late in a theta rhythm and systematically advances as the field is exited has interesting implications for the manner in which different cells with adjoining place fields become associated. For simplicity, assume an organism runs from place field A into place field B. Because field A is entered before field B, the cell associated with field A must fire at the same time or before (but within the temporal window normally associated with LTP) that associated with field B to preserve sequence information. Thus, as pointed out by O'Keefe and Recce (1993), maximum potentiation should occur when the two place fields completely overlap. If the rate of phase advance is the same in both cells and LTP occurs if cells fire within a temporal window of one-half theta cycle, than potentiation should occur when firing in cell A precedes that in cell B by a minimum. This occurs in our model in a periodic fashion with each theta cycle assuming an approximately constant velocity of movement through the field. In other words, as place field B is shifted temporally from place field A, the likelihood for potentiation decreases until the amount of place field shift corresponds to approximately one theta cycle, at which time the possibility for LTP should increase again for a half-cycle. After this half-cycle, the chance for LTP again decreases until the next shift in place field occurs that corresponds to approximately a theta cycle. Note that the likelihood of LTP also decreases overall in that as the fields become less overlapping spatially, the likelihood of temporal coincidence of firing between these different place cells decreases. Consequently, in addition to providing information about an animal's location, it appears that the timing properties observed in the phase precession of place cell firing may also play an important role in the way synaptic modifications take place in the hippocampus.

APPENDIX

Spatial distribution and density of ionic conductances

Tables 1 and 2 list the maximum ionic conductance densities (mS/cm^2) by channel type and compartment for both pyramidal cells and interneurons. Equations for each of the conductances can be found in Traub et al. (1991, 1992).

Synaptic delays and weights, connection probabilities, and conduction velocities

A conduction velocity of 0.5 m/s was used for pyramidal cell axons, in keeping with experimental observations (Miles 1988). Interneurons were assumed to be more locally constrained (Seress and Ribak 1985). Both the synaptic delay and connection probability between two cells depended on the distance from the presynaptic cell. The probability of a presynaptic cell connecting a postsynaptic cell was determined by a Gaussian distribution centered at the presynaptic cell (Li et al. 1994). The percentage of connectivity among pyramidal cells (p) and interneurons (i) in the network was as follows: $p \rightarrow p = 15\%$ (each pyramidal cell contacted 15% of the other pyramidal cells in the network); $p \rightarrow i = 20\%$; $i \rightarrow p = 30\%$; $i \rightarrow i = 20\%$. Synaptic weights were initialized with the use of a uniform distribution before learning.

Synaptic conductances and time constants

The spatial distribution of each synaptic conductance is shown in Fig. 1*B*. The maximum conductance, rise and decay time constants, and reversal potentials for each synaptic current are given below. Each synaptic conductance was modeled with the use of a dual exponential (see METHODS), with the exception of the NMDA-receptor-mediated conductance (Table 3) (Zador et al. 1990).

Electrotonic parameters

The unit membrane resistance (R_i) for both the pyramidal cells and interneurons was 10,000 Ω/cm^2. The unit axial resistance (R_i) for both cell types was 100 Ω/cm. Unit capacitance (C_m) was 3 $\mu F/cm^2$ for pyramidal cells, leading to a 30-ms membrane time constant, and 1 $\mu F/cm^2$ for interneurons, leading to a 10-ms membrane time constant (Traub et al. 1991). Electrotonic length of the basilar and apical dendrites in all cells was 0.8 and 1.0 λ, respectively (Traub et al. 1991).

TABLE 1. *Pyramidal cell*

Compartment	g_{Na}	g_{Ca}	$g_{K(DR)}$	$g_{K(AHP)}$	$g_{K(Ca)}$	$g_{K(A)}$	$g_{K(leak)}$
Apical 2	0.0	9.0	0.0	0.8	8.5	0.0	0.1
Apical 1	15.0	9.0	10.0	0.8	18.0	0.0	0.1
Soma	30.0	4.0	15.0	0.8	10.0	5.0	0.1
Basal 2	7.5	10.0	10.0	0.8	17.0	0.0	0.1
Basal 1	0.0	7.0	0.0	0.8	6.5	0.0	0.1

TABLE 2. *Interneuron*

Compartment	g_{Na}	$g_{K(DR)}$
Apical 2	0.0	0.0
Apical 1	0.0	0.0
Soma	500.0	250.0
Basal 2	0.0	0.0
Basal 1	0.0	0.0

Calcium buffering

The internal calcium concentration ($[Ca^{2+}]_i$) was calculated for a depth of 100 nm beneath the surface of the cell. A simple linear diffusion model was adopted to describe the time-dependent variation of this quantity (McCormick and Huguenard 1992; Traub et al. 1991). The discretized equation used to calculate internal calcium can be expressed as

$$[Ca^{2+}]_{i_t} = [Ca^{2+}]_{i_{t-1}} + dt\{(-5.18 \times 10^{-3} I_{Ca})/(\text{area} \cdot \text{depth}) - \beta[Ca^{2+}]_{i_{t-1}}\} \quad (7)$$

where -5.18×10^{-3} is a constant used to convert current (nA), time (ms), and volume (μm^3) into $[Ca^{2+}]_i$ ion concentrations, and $\beta = 0.1$/ms scales the rate of diffusion.

$GABA_B$-receptor-mediated suppression of EPSPs and IPSPs

The suppression of EPSPs and IPSPs was modeled as a downregulation of synaptic release due to the activation of $GABA_B$ autoreceptors on the terminal endings of pyramidal cells and interneurons (Howe et al. 1987; Potashner 1979). Two components were included in this portion of the model: *1*) calculation of a local concentration of GABA ($[GABA]_o$) in the estimated neighborhood of the terminal endings of the presynaptic cell (because we have not modeled axons explicitly in our model, this estimation is simply based on the locations of all the postsynaptic cells connected to the presynaptic cell); and *2*) downregulation of the postsynaptic potentials at intrinsic fibers in proportion to the local value of $[GABA]_o$. There were two sources of GABA at any given location, including rhythmic firing of cells in the medial septum, which preferentially innervate interneurons (Freund and Antal 1985), and local interneuron activity. For simplicity, we assume that a local concentration of GABA decays according to first-order kinetics. Thus at each location the value for the local GABA concentration, $[GABA]_o$, was given by

$$d[GABA]_o/dt = c\lambda_{pre} - \gamma[GABA]_o \quad (8)$$

where $c = 7.5 \times 10^{-2}$ is a constant used to convert the number of GABA-containing, active (spiking) presynaptic cells connected to the postsynaptic cell (λ_{pre}), time (ms), and volume (μm^3) into $[GABA]_o$ values, and $\gamma = 0.8$/ms is the rate of diffusion. The local GABA concentration was then used to downregulate the postsynaptic potentials in that cell by reducing the synaptic currents (AMPA- and NMDA-receptor-mediated for EPSPs and $GABA_A$- and $GABA_B$-receptor-mediated for IPSPs), influencing it in proportion to the local concentration of GABA, $\alpha[GABA]_{o_t}$, at time *t*.

TABLE 3. *Reversal potentials*

Receptor	g_{max}, nS	τ_1, ms	τ_2, ms	Reversal, mV
AMPA	0.5	2.0	2.0	0.0
$GABA_A$	4.5	1.0	8.0	−60.0
$GABA_B$	2.7	35.0	100.0	−75.0

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