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Theta Oscillations in the Hippocampus

Review

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Theta oscillations represent the "on-line" state of the hippocampus. The extracellular currents underlying theta waves are generated mainly by the entorhinal input, CA3 (Schaffer) collaterals, and voltage-dependent Ca^{2+} currents in pyramidal cell dendrites. The rhythm is believed to be critical for temporal coding/decoding of active neuronal ensembles and the modification of synaptic weights. Nevertheless, numerous critical issues regarding both the generation of theta oscillations and their functional significance remain challenges for future research.

Functions of a brain structure can be deduced from correlation and perturbation methods. Convergence of these methods at different levels of analysis indicates that the hippocampus and associated structures serve to generate long-term memory traces. Clinical evidence indicates that damage to the hippocampus produces anterograde amnesia. At the cellular-molecular level, the intricacies of synaptic plasticity, a candidate model for memory storage, are being studied in great detail (cf. Kandel and Squire, 2000). However, the link between single neuron computation and computation at the network level is poorly understood. It remains unclear how neuronal cooperativity in intact networks relates to memories or how network activity in the behaving animal brings about synaptic modification. Because network patterns arise from the collective action of neurons, some of their behavior-related changes can be studied by recording the current flow in the extracellular space. A prominent network pattern in the hippocampus of all mammals studied to date, including humans (Arnolds et al., 1980; Kahana et al., 1999; Tesche and Karhu, 2000; Bódizs et al., 2001), is a slow oscillation in the theta-alpha frequency band. Key issues therefore are to understand how theta oscillation can group and segregate neuronal assemblies and to assign various computational tasks to them. An equally important task is to reveal the relationship between synaptic activity (as reflected globally by field theta) and the output of the active single cells (as reflected by action potentials). A goal of this review is to summarize new knowledge about the cellular-synaptic generation of theta waves and the importance of theta oscillations in the coordination of neuronal networks and in the modification of synaptic connections. Several excellent reviews have been published on the physiology and pharmacology of theta oscillations (Bland, 1986; Vanderwolf, 1988; Lopes da Silva et al., 1990; Buzsáki et al., 1994; Stewart and Fox, 1990; Vinogradova, 1995; Vertes and Kocsis, 1997). The theta models discussed in previous reviews utilize neurons with passive cable properties. During the past several years, it has become increasingly clear that neurons are endowed with a host of active conductancies and intrinsic oscillatory properties (Llinás, 1988; Häusser et al., 2000). A further goal of this review therefore is to integrate this new knowledge with network level information and propose new research directions for understanding the functional significance of the theta rhythm.

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Brain Systems Involved in the Generation of Theta Oscillations

Theta oscillations depend on ongoing behavior (Grastyán et al., 1959; Vanderwolf, 1969). Although no consensus has yet emerged regarding their specific behavioral correlates, theta waves are most consistently present during REM sleep (Jouvet, 1969) and during various types of locomotor activities described by the subjective terms "voluntary," "preparatory," "orienting," or "exploratory" (Vanderwolf, 1969). In general, theta waves are absent in the immobile animal but short epochs of theta trains can be elicited by noxious conditioned stimuli (cf. Bland, 1986). Theta waves have been also assumed to be carriers of mnemonic processes (Miller, 1989; Lisman and Idiart, 1995; Raghavachari et al., 2001). It should be noted here that field oscillations at theta/alpha frequencies have been observed in numerous cortical structures (Steriade, 2000). Intracranial recordings in humans indicate, however, that these patterns occur in different behavioral states and are not coherent with hippocampal theta waves (Kahana et al., 1999; Raghavachari et al., 2001). Thus, the relevance of these rhythms to theta oscillations present in the hippocampus and associated structures has yet to be established.

In the discussion of the mechanisms of oscillations, it is useful to distinguish two terms. The term "current generator" refers to the transmembrane currents responsible for the magnitude of the recorded field. On the other hand, "rhythm generator" refers to mechanisms responsible for the emergence and control of the oscillatory pattern and frequency. Brain regions with parallel arranged dendrites and afferents, such as cortical structures, give rise to large amplitude extracellular potentials, whereas subcortical nuclei with less orderly spatial organization generate "closed fields," i.e., small-amplitude field events.

Theta oscillation is most regular in frequency and largest amplitude in the str. lacunosum-moleculare of the hippocampal CA1 region. Both the amplitude and phase of theta waves change as a function of depth (i.e., different layers; Figure 1), whereas in the same layers they are robustly similar along the long axis of the hippocampus (Bullock et al., 1990). Theta oscillations are also present in the dentate gyrus and the CA3 region. In addition to the hippocampal formation, theta frequency oscillations and phase-locked discharge of neurons to theta waves have been observed in several other structures, including the subicular complex, ento-

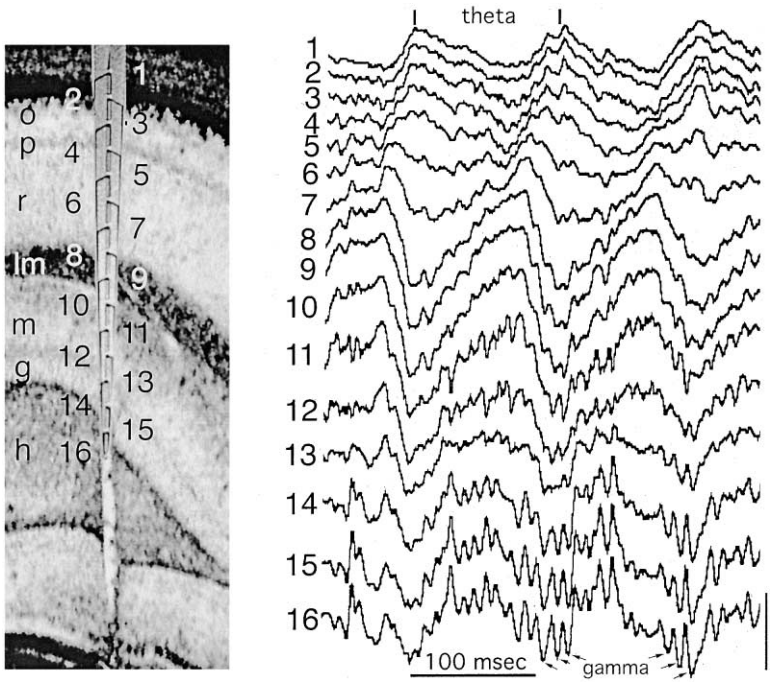

Figure 1. Voltage-versus-Depth Profile of Theta Oscillation in the Rat

(Left) A 16-site silicon probe in the CA1-dentate gyrus axis. Numbers indicate recording sites (100 μm spacing). o, str. oriens; p, pyramidal layer; r, str. radiatum; lm, str. lacunosum-moleculare; g, granule cell layer; h, hilus. (Right) Theta waves recorded during exploration. Note gradual shift of theta phase from str. oriens to str. lacunosum-moleculare. Gamma waves superimposed on theta oscillation are marked by arrows. Vertical bar: 1 mV. (From Bragin et al., 1995.)

rhinal cortex, perirhinal cortex, cingulate cortex, and amygdala (Adey, 1967; Mitchell and Ranck, 1980; Alonso and Garcia-Austt, 1987; Leung and Borst, 1987; Paré and Collins, 2000). These structures are thus the main current generators of the extracellularly recorded theta field. However, none of these cortical structures are capable of generating theta activity on their own.

Several subcortical nuclei have been postulated to be critically involved in the rhythm generation of theta. Afferents from these nuclei release neurotransmitters that may allow for the emergence of network oscillations in the hippocampus and associated structures ("permissive" action) or may provide a coherent, theta frequency output ("pacemaker" function). Because lesion or inactivation of medial septum-diagonal band of Broca (MS-DBB) neurons abolishes theta waves in all cortical targets, it has been regarded as the ultimate rhythm generator of theta (Petsche et al., 1962). The MS-DBB is reciprocally connected to the supramammillary region (Borhegyi and Freund, 1998; Leranth et al., 1999), a second critical structure involved in pacing the theta rhythm (cf. Vertes and Kocsis, 1997). Whether the MS-DBB and supramammillary nucleus are true pacemakers or rhythmic firing of their neurons depends on the hippocampal and entorhinal feedback has yet to be determined (Lee et al., 1994; Brazhnik and Fox, 1999; King et al., 1998; Borisyuk and Hoppensteadt, 1999; Denham and Borisyuk, 2000; Wang, 2002).

Neurons in several other subcortical structures are phase locked to hippocampal theta oscillation, including the dorsal raphe nucleus, ventral tegmental nucleus of Gudden, and anterior thalamic nuclei (cf. Bland, 1986; Vertes and Kocsis, 1997). Finally, stimulation of several subcortical nuclei elicits hippocampal theta (cf. Bland, 1986). However, these latter structures also project to the thalamus and/or neocortex as well, and they are part of a common ascending activation system (Moruzzi and Magoun, 1949) rather than structures specifically involved in theta rhythm generation. In summary, the minimum conditions necessary for the generation of oscillating extracellular currents in the theta frequency band are the proper connections between the hippocampus and MS-DBB. Despite 40 years of research (Petsche et al., 1962), however, the exact physiological mechanisms of these interactions have remained unresolved.

"Classic" Theta Model and Its Inadequacies

In the first and simplest theta model, the MS-DBB has been postulated to be the rhythm generator (pacemaker), which supplies phasic modulation to the hippocampus (Petsche et al., 1962). Subsequent models added new components that are summarized in Figure 2. On the assumption that the extracellular field is generated by the summed activity of IPSPs and EPSPs on the somata and dendrites of principal cells, respectively, these models utilized a single canonical CA1 pyramidal cell with passive membrane properties. It has been assumed that all pyramidal cells receive coherent excitatory (from perforant path) and inhibitory (from septum to feed-forward inhibitory neuron) inputs. The interplay between these two current generators (dipoles) is assumed to be responsible for the unique amplitude/phase versus depth profiles of hippocampal theta oscillation. According to this scheme, the most strongly excited minority of the population would discharge at the same time when nonspiking neurons are maximally depolarized, justifying the "lumped" model. As Figure 1 illustrates, theta waves in the waking rat show a gradual phase reversal between CA1 str. oriens and the hippocampal fissure (Winson, 1974), consistent with the coordinated activity of at least two current generators (dipoles). Because the largest amplitude theta waves are observed at the hippocampal fissure, rhythmic excita-

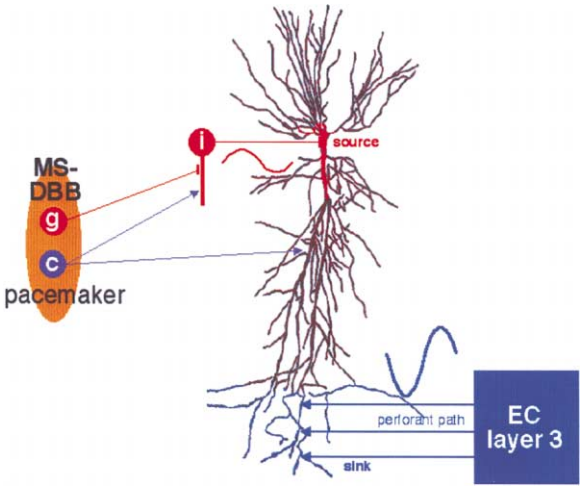

Figure 2. "Classic" Model of Extracellular Theta Current Generation

The medial septum and diagonal band of Broca (MS-DBB) area are assumed to be the rhythm generator (pacemaker) of theta. Cholinergic neurons (c) provide slow depolarization of their target pyramidal cell and basket interneuron (i). MS-DBB GABAergic neurons (g) rhythmically hyperpolarize the basket interneuron (i). In turn, the rhythmic IPSPs in the pyramidal cell are assumed to induce perisomatic currents (red; inhibitory theta dipole). Rhythmic EPSPs from the entorinal cortex (EC) are responsible for the active sink in the distal dendritic region (blue; excitatory theta dipole). The relative magnitude and phase relationship of the inhibitory (somatic) and excitatory (distal dendritic) dipoles are hypothesized to determine the unique amplitude and phase versus depth distribution of theta waves in the CA1 region. (Adapted from Holsheimer et al., 1982; Buzsáki et al., 1983; Leung, 1984; Stewart and Fox, 1990; Lee et al., 1994.)

tion of the distal dendrites by the entorhinal afferents is assumed to play the most important role in the current generation of extracellular field theta.

A second theta dipole in the CA1 region is assumed to be generated by somatic IPSPs. These IPSPs are brought about by the γ frequency discharge of basket and chandelier cells, repeated at theta frequency (Artemenko, 1972; Fox, 1989; Leung and Yim, 1986; Ylinen et al., 1995; Kamondi et al., 1998a). The rhythmic drive and/or inhibition of basket cells may arrive from the MS-DBB (Buzsáki et al., 1983; Stewart and Fox, 1990), although several other inputs, including the entorhinal afferents, CA3 afferents, CA1 recurrent collaterals, and other interneurons with intrinsic oscillatory properties, may also be involved. Current-source density (CSD) analysis (Mitzdorf, 1985), showing a strong sink in the CA1 str. lacunusom-moleculare and a source in the pyramidal layer also support the above scheme (Buzsáki et al., 1986; Brankack et al., 1993). The gradual phase shift of the theta waves with depth (Winson, 1974) and the lack of a clear "null" zone are explained by the phase-shifted nature of the somatic and dendritic dipoles (Buzsáki et al., 1983; Leung, 1984).

Research over the past several years points out several inadequacies of the above model. (1) Although both CSD analysis and unit recording studies suggest that dendritic excitation is coupled to somatic inhibition (Figures 3 and 4; Csicsvari et al., 1999), in the classic theta model a controversy exists between the timing of the excitatory and inhibitory inputs as postulated from field/CSD studies and the actual discharge of the pyramidal cells and interneurons. If the major excitatory drive during theta is the entorhinal input, CA1 pyramidal cells are expected to discharge maximally at the peak of the sink in str. lacunosum-moleculare. However, the highest probability of discharge in the behaving rat occurs around the positive peak of theta recorded at the level of the distal dendrites, corresponding to the negative phase of the theta waves in the pyramidal layer (Figure 3A; Fox et al., 1986; Buzsáki et al., 1986; Brankack et al., 1993; Csicsvari et al., 1999). (2) Another finding, which is at odds with the classic model, is that the theta phase relationship of pyramidal cells is not fixed but changes dynamically as a function of behavior (O'Keefe and Recce, 1993; Skaggs et al., 1996). (3) Recent work indicates that pyramidal neurons in various limbic structures are endowed to oscillate at theta frequency. These intrinsic mechanisms may be as important in the generation of transmembrane currents as postsynaptic potentials. (4) The complex interconnections among the numerous hippocampal interneuron classes pose further questions about their involvement in rhythm generation. (5) Importantly, more recent knowledge indicates that the recurrent circuit of the CA3 region may function as an intrahippocampal theta oscillator. (6) Finally, the mutual connections between MS-DBB and the hippocampus/entorhinal cortex indicate that the "septal pacemaker"-"hippocampal follower" model is overly simple. We will discuss these topics below. Some potential solutions will be offered whereas answers to several other issues will require further experimentation.

Transmitters and Receptors Responsible for Theta Oscillations: Roles for Cholinergic, $GABA_A$, and NMDA Receptors

Drugs affecting the field theta waves may interfere with the rhythm and/or the current generators. For example, blockade or potentiation of $GABA_A$ receptors during picrotoxin-induced epilepsy or pentobarbital anesthesia, respectively, eliminates theta by affecting both rhythm generation and current generation. In principle, every afferent pathway with phase-locked activity to the global rhythm contributes to the extracellular field. Given the large number of structures affecting theta oscillations, it is not surprising that theta activity can be influenced by a variety of drugs (Vanderwolf, 1988). Vanderwolf (Kramis et al., 1975) suggested that, on the basis of pharmacological sensitivity, two types of theta could be distinguished: atropine-sensitive and atropine-resistant. The idea of an atropine-sensitive form of theta comes from early observations that muscarinic blockers, such as atropine, completely eliminate theta oscillations in anesthetized animals. In contrast, in the awake, walking rat, the amplitude and frequency of theta oscillation do not substantially change even after large doses of systemically administered muscarinic blockers, although the wave shape and depth profile of theta under atropine are quantitatively different from those in the drug-free animal (Buzsáki et al., 1986). This persisting form of theta is referred to as "atropine resistant" (Vanderwolf, 1988). The neurotransmitter(s) and receptor(s) responsible for the atropine-resistant type of theta have

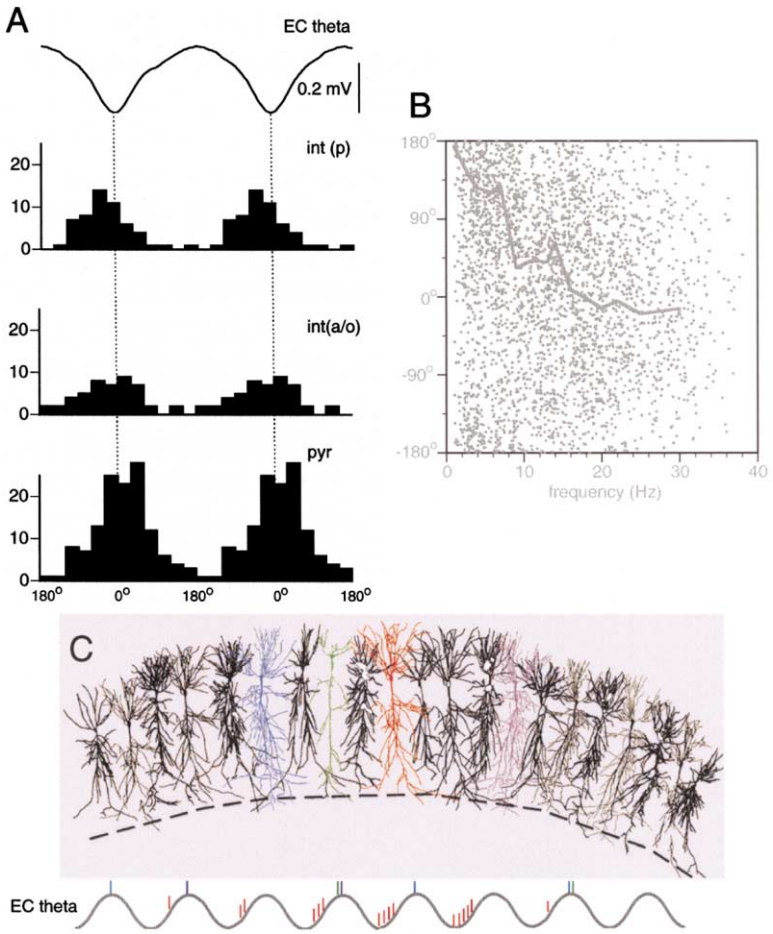

Figure 3. Theta Phase Relationship of Pyramidal Cell Spiking Is Variable

(A) Averaged field theta wave and the preferred phase distribution of single interneurons in the pyramidal layer [int(p)] and alveus-str. oriens [int(a/o)] and CA1 pyramidal cells of the rat. Only neurons with significant phase modulation are included. Note that most interneurons and pyramidal cells discharge on the negative phase of local (pyramidal layer) theta waves. (B) Relationship between firing rate and theta phase distribution of spikes for a single pyramidal neuron. Line: running circular mean. The phase was calculated for each firing rate bin separately. Note the half-cycle phase shift from $<$2 Hz to $>$15 Hz. (C) Illustration of spike-phase relationship for weakly and strongly activated neurons. The strongly activated neuron (due to hypothesized coactivation by the entorhinal and Schaffer afferents; red) discharges on the negative phase of local extracellular (EC) theta. Neurons with threshold activation discharge on the positive phase (blue, green, and purple cells). Nonspiking cells are black. The strongly active few pyramidal cells thus may contribute more action potentials per theta cycle than the remaining population combined. (From Csicsvari et al., 1999 and unpublished data from K. Harris, H. Hirase, X. Leinekugel, and G.B.)

never been identified conclusively (Vanderwolf, 1988; Vertes and Kocsis, 1997).

Complete surgical removal of the entorhinal cortex or surgical isolation of the entorhinal cortex from its nonhippocampal afferents eliminates the theta dipole localized on the banks of the hippocampal fissure (Figure 4). Importantly, such lesions render the remaining theta oscillation atropine sensitive (Buzsáki et al., 1983; Vanderwolf and Leung, 1983) and its depth versus voltage profile somewhat similar to that observed under urethane anesthesia (Ylinen et al., 1995; Kamondi et al., 1998a). Two important hypotheses can be deduced from these observations. First, that the receptors involved in atropine-resistant type of theta are urethane sensitive (Kramis et al., 1975). The second deduction is that the atropine-resistant component of hippocampal theta is conveyed by layer III and layer II entorhinal cortical afferents to the CA1 and dentate/CA3 neurons, respectively (Amaral and Witter, 1989). Since these pathways contain glutamate (cf. Bland, 1986) and urethane attenuates glutamate release from presynaptic vesicles (Moroni et al., 1981), one might expect quantitative similarities between the CSD maps of theta and those evoked by electrical stimulation of the entorhinal afferents. However, the theta dipoles mediated by the entorhinal cortex cannot be fully explained by glutamate activation of pyramidal and granule cells via fast acting AMPA receptors only (Buzsáki et al., 1986; Brankack et al., 1993; Bragin et al., 1995).

We hypothesize that activation of NMDA receptors is critical for the atropine-resistant form of theta oscillation. Although the pharmacological action of urethane is not well understood, experiments using more specific drugs provide support for this hypothesis. First, the depth versus voltage profile of theta under the NMDA receptor blocker, ketamine, is similar to that described under urethane (Soltesz and Deschénes, 1993). Second, combination of ketamine or other NMDA receptor blockers (phencyclidine, 3-(2-carboxypiperazin-4-yl) propyl-1-phosphonic acid [CPP], DL-2-amino-5-phosphonovaleric acid [APV]) and atropine or scopolamine abolished all theta activity in the hippocampus (Vanderwolf and Leung, 1983; Soltesz and Deschénes, 1993; Horvath et al., 1988). Earlier experiments, using anesthetic doses of urethane or NMDA blockers, reported that the frequency of atropine-sensitive theta is substantially less (2–5 Hz) than in the awake rat (6–9 Hz). However, subanesthetic doses of NMDA receptor blockers or their intracerebro-ventricular application are also effective in reducing the atropine-resistant theta component (Horvath et al., 1988; L.S. Leung, unpublished observations). A candidate target of the NMDA blockers is the entorhinal afferent synapses on the distal apical dendrites of CA1 pyramidal neurons. These synapses have at least two distinguishing features. First, they are larger than the synapses in str. oriens and radiatum and are frequently perforated (Megias et al., 2001). Second, in addition to spines, the terminals frequently contact dendritic shafts. Activation

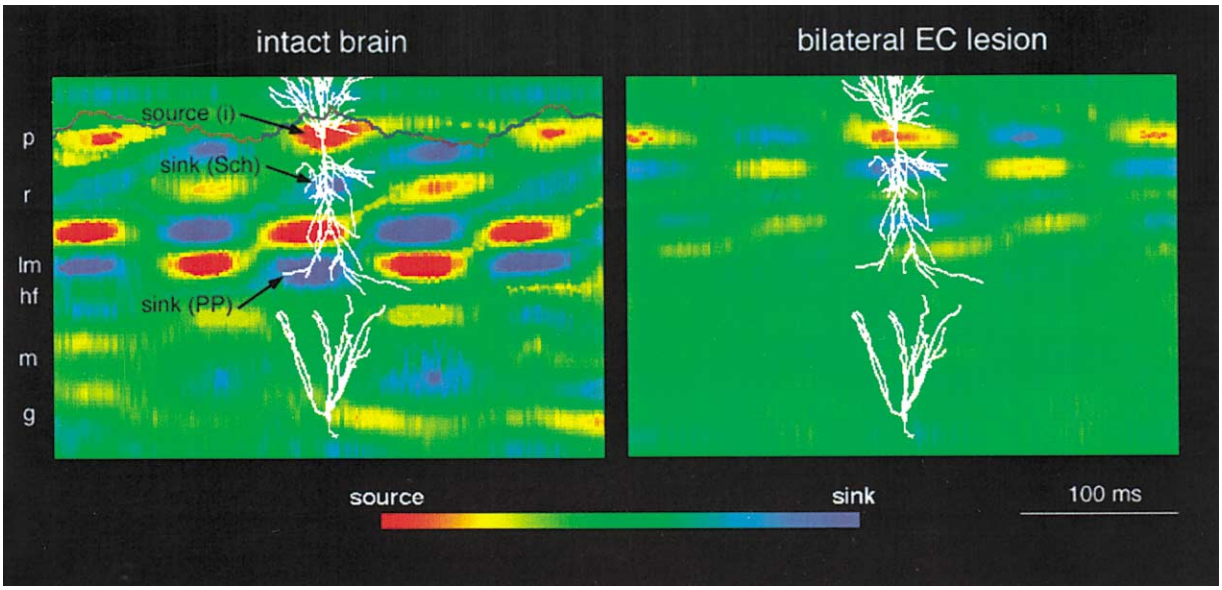

Figure 4. Entorhinal Cortex-Mediated Theta Dipole in the Hippocampus

The simultaneously obtained field potentials (see Figure 1) were converted to one-dimensional current-source density (CSD) maps. Left: intact rat. Voltage trace of theta recorded in the CA1 pyramidal layer is superimposed for reference (gray trace). Rhythmic sources (red) in the pyramidal layer (p) are coupled to rhythmic sinks (blue) in the stratum lacunosum-moleculare (lm) representing a putative inhibitory source (l) and excitation by the perforant path input (PP). An additional sink, mediated by the Schaffer collaterals of CA3 pyramidal cells (Sch), is present in str. radiatum (r). Right: same animal 2 days after bilateral removal of the entorhinal cortex (EC). Note the absence of sink at the distal dendrites and the survival of the more proximal source-sink pair. The same time and color scales apply to both CSD maps. m, molecular layer; g, granule cell layer. (From Kamondi et al., 1998a.)

of the NMDA receptors on the distal apical dendrites may be brought about by theta phase-locked Ca^{2+} potentials in distal dendrites of discharging CA1 pyramidal neurons (Figure 5). Furthermore, in vitro experiments also indicate that the entorhinal input has a greater NMDA component than the associational (CA3) input to CA1 pyramidal cells (Otmakhova and Lisman, 2000). Although NMDA receptors in the hippocampus are usually associated with synaptic plasticity (Kentros et al., 1998), these findings indicate that NMDA receptors located on the distal apical dendrites are also important in spontaneous synaptic events and the maintenance of synaptic function (Kovalchuk et al., 2000).

The precise targets of systemic atropine in hippocampal theta generation are unknown. The remaining theta sinks and sources after bilateral lesion of the entorhinal cortex

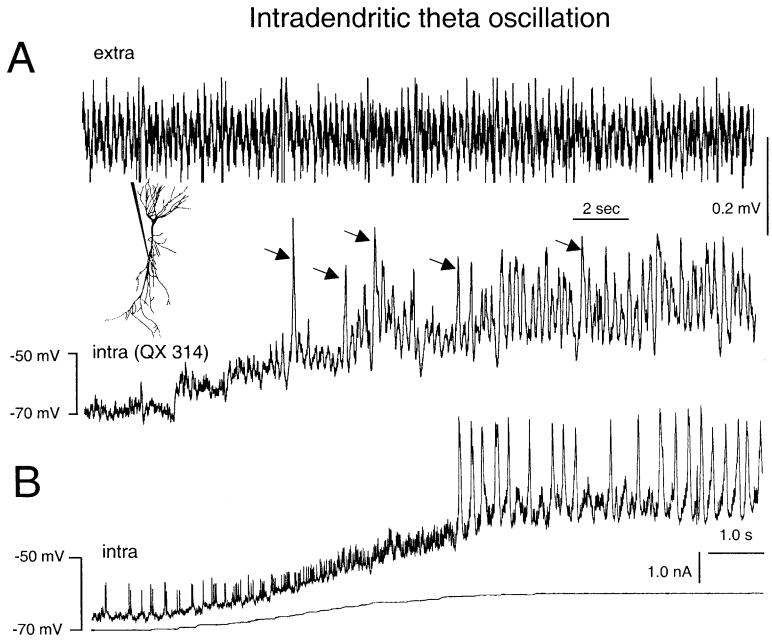

Figure 5. Voltage-Dependent Theta Oscillation in Pyramidal Cell Dendrites In Vivo

(A) Continuous recording of extracellular (extra; CA1 pyr layer) and intradendritic (intra) activity in the rat. Holding potential was manually shifted to progressively more depolarized levels by intradendritic current injection. Inset: location of the dendritic penetration. The recording electrode contained QX 314 to block fast (Na^{+}) spikes. Some of the high-threshold Ca^{2+} spikes are marked by arrows. (B) Another dendritic recording without QX 314 (370 μm from pyramidal layer). Note large amplitude Ca^{2+} spikes and small amplitude fast spikes. (Reprinted from Kamondi et al., 1998a.)

are more compatible with associational/commissural inputs and perisomatic inhibition than with the distribution of septo-hippocampal cholinergic terminals, which are present in all layers (Kamondi et al., 1998a). This observation suggests that cholinergic-muscarinic receptors in the hippocampus are not responsible directly for the extracellular theta currents. Furthermore, cholinergic activation of M1 receptors of pyramidal cells is much too slow (Cole and Nicoll, 1983; Hasselmo and Fehlau, 2001) for the generation of theta-associated cyclic membrane potential changes. Release of acetylcholine may simply depolarize pyramidal cells and interneurons (Madison et al., 1987) and/or affect voltage-dependent conductancies, such as I_M, I_h, and I_A (Hoffman et al., 1997). Muscarinic receptors are both synaptic and extrasynaptic and are present on presynaptic boutons of both glutamatergic and GABAergic axons (Hasselmo and Schnell, 1994; Vizi and Kiss, 1998; Hájos et al., 1998). Furthermore, muscarinic blockers can affect receptors in both MS-DBB and hippocampus. We therefore conclude that EPSPs brought about by the MS-DBB cholinergic neurons on hippocampal pyramidal cells cannot be responsible for the atropine-sensitive form of theta.

An alternative mechanism to the direct excitation of pyramidal cells by acetylcholine in theta generation (Petsche et al., 1962) is the cholinergic modulation of interneurons (Buzsáki et al., 1983; Stewart and Fox, 1990). Tonic cholinergic excitation of interneurons, coupled with their phasic septal GABAergic inhibition, has been suggested to be responsible for the rhythmic discharge of hippocampal interneurons (Freund and Antal, 1988; Stewart and Fox, 1990). In turn, the theta frequency discharge of the interneurons imposes rhythmic IPSPs on their target principal cells (Fox, 1989; Soltesz and Deschénes, 1993; Ylinen et al., 1995; Cobb et al., 1995; Tóth et al., 1997; Kamondi et al., 1998a). According to this hypothesis, the theta waves observed in the anesthetized animal and in the entorhinal cortex-damaged brain should represent mainly somatic outward currents and would be localized close to the pyramidal layer (Figure 2; Buzsáki et al., 1983; Leung, 1984). Alternatively, the theta dipoles, which remain after removing the entorhinal inputs (Figure 4), can be accounted for by the more proximal dendritic excitation of CA1 pyramidal cells by the associational (Schaffer) collaterals. This interpretation assumes that the atropine-sensitive form of theta emerges in the CA3 recurrent collateral system (Kocsis et al., 1999).

It should be spelled out that there is an unresolved discrepancy between the pharmacological blockage of the muscarinic M1 receptors and the absence of MS-DBB cholinergic neurons. Whereas the amplitude of hippocampal theta is only modestly affected after atropine treatment, it is reduced several-fold after selective neurotoxin elimination of MS-DBB cholinergic cells (Lee et al., 1994). This discrepancy suggests that muscarinic M2 (Hájos et al., 1998) and/or nicotinic receptors (Ji and Dani, 2000) may also be involved in the regulation of theta. Because the atropine-resistant type of theta in the hippocampus is conveyed by the entorhinal input, the theta generated in the entorhinal cortex is likely not affected by muscarinic blockade. On the other hand, lesion of the MS-DBB abolishes theta oscillations in the entorhinal cortex as well. It is possible therefore that the theta generation in the entorhinal cortex depends on nicotinic receptors (but see Whishaw, 1976).

Contribution of the Dentate Gyrus and CA3 Recurrent Collateral System to Theta Generation

Neurons in all hippocampal regions are phase modulated by theta oscillation (Bland et al., 1975; Buzsáki et al., 1983; Fox et al., 1986). Therefore, both the numerous granule cells and CA3 pyramidal cells are expected to generate their own theta fields.

Although theta phase does not fully reverse across the granule cell layer, the waves recorded in the outer molecular layer and the hilus are phase shifted by approximately 90° (Buzsáki et al., 1983). Furthermore, large phase jumps (180°) have been described in the molecular layer (Buzsáki et al., 1986). If the neighboring excitatory dipoles, formed presumably by afferents originating in the medial and lateral entorhinal cortex and the hilar mossy cells (Amaral and Witter, 1989), overlap in phase, the extracellular currents may be cancelled or reduced. The relatively smaller contribution of granule cells to the overall hippocampal theta field is illustrated further by the observation that elimination of granule cells by neonatal X-ray irradiation does not change the depth versus voltage profile of theta waves appreciably in the anesthetized rat (Whishaw et al., 1978). In contrast, elimination of CA1 pyramidal neurons by forebrain ischemia results in a dramatic decrease of theta amplitude (Monmaur et al., 1986; Buzsáki et al., 1990).

The CA3 pyramidal cells contribute to theta fields recorded in both the CA3 and CA1 regions. The CA3 output contributes directly to the theta field recorded in the CA1 region, as demonstrated by a sink in CA1 str. radiatum (Figure 4; Buzsáki et al., 1986; Brankack et al., 1993). The small magnitude of the sink is explained by the observation that only a small percentage of CA3 pyramidal cells are active during a given theta cycle. Nevertheless, this minority appears to be critical for the discharge of target CA1 neurons because CA3 pyramidal cells are active on the same phase of theta as CA1 pyramidal cells (Fox et al., 1986; J. Csicsvari and G.B., unpublished data).

Despite the similar cytoarchitecture of the CA1 and CA3 regions, the extracellular theta currents in the CA3 region are considerably smaller than in CA1. Several factors may be responsible for this conspicuous difference. First, the distal dendritic arbor of CA3 pyramidal cells is considerably smaller than that of the CA1 pyramidal neurons (Turner et al., 1995; Pyapali et al., 1998). Second, in addition to the inputs common to CA3 and CA1, CA3 pyramidal neurons receive perisomatic excitation near their somata from the large mossy terminals of granule cells (cf. Henze et al., 2000). The currents induced by the mossy boutons flow in a direction opposite to the currents generated by the perforant path and the recurrent collaterals, leading to a potentially large reduction of extracellular currents. Finally, the excitatory drive from the entorhinal layer II and layer III neurons to CA3 and CA1 pyramidal cells may be different. Recording from identified neurons in the entorhinal cortex in the behaving rat will be required to address this latter issue.

While the CA1 and dentate regions act only as current generators of theta, recent findings indicate that the CA3 recurrent collateral system can also act as a rhythm generator. After surgical removal of the entorhinal cortex, all remaining theta appears to depend on the integrity of the CA3 region, and theta signals in all layers are highly coherent with each other (Bragin et al., 1995). In contrast, the coherence of theta signals in CA1 str. radiatum and str. lacunosum-moleculare in the intact brain is low and the powers of theta signals in these layers are inversely correlated with each other (Kocsis et al., 1999). On the other hand, theta waves in CA1 str. radiatum and in the inner third of the dentate molecular layer are strongly related. Since these layers are the targets of the intrahippocampal associational projections (Amaral and Witter, 1989), the findings suggest that the recurrent network of CA3 pyramidal cells and possibly hilar mossy cells forms an intrahippocampal oscillator. The intrahippocampal theta oscillator requires cholinergic activation because in the absence of the entorhinal input, the remaining theta is abolished by atropine.

The notion that the cholinergic component of theta emerges in the CA3 recurrent collateral system implies that this form of oscillation can also be studied in the isolated hippocampus. To this end, Konopacki et al. (1987; Bland et al., 1988) observed that when a hippocampal slice is bathed in a solution containing the muscarinic drug carbachol, short bursts of field oscillations at 4 to 15 Hz occur intermittently. Depending on the concentration of the drug, the magnitude of the field oscillation and the synchrony of the neuronal population vary from in vivo theta-like pattern to overt epileptic patterns (Williams and Kauer, 1997). At a low dose (<5 μM), field oscillation may not be evident, although some CA3 pyramidal neurons may show sustained subthreshold membrane potential oscillation at 5 to 15 Hz. Moderate doses (15–40 μM) induce field oscillations and associated discharge of pyramidal neurons (Fellous and Sejnowski, 2000). The carbachol-induced rhythm is generated in the CA3 region and attenuated by AMPA receptor blockers. In the CA1 region, theta waves are reversed in phase in the str. oriens/pyramidale and str. radiatum. Although some interneurons are entrained by the network rhythm (Pitler and Alger, 1992; McMahon et al., 1998), they are not essential for the maintenance of the rhythm (MacVicar and Tse, 1989; Traub et al., 1992; Fellous and Sejnowski, 2000), a main difference from the in vivo situation. Similar oscillatory patterns have also been observed in the organotypic hippocampal slices and in hippocampus-septum cocultures (Fischer et al., 1999). In the combined cultures, enhancement of spontaneously released acetylcholine levels, by blocking the enzyme acetylcholine esterase, is sufficient for the production of theta-like network oscillation (Fischer et al., 1999).

The mechanisms by which theta-like oscillations emerge in the hippocampal slice preparation have yet to be disclosed. Pyramidal neurons are endowed with intrinsic properties to oscillate at theta frequency (see below). Appropriate activation of such intrinsic oscillatory mechanism may elicit theta rhythm in single cells. Acetylcholine or carbachol induces dendritic depolarization and can affect several K^+ and other channels (I_h, I_A, I_{AHP}, I_M, and $I_{K[Ca]}$); Madison et al., 1987; Fellous and Sejnowski, 2000). When the oscillating cells communicate with each other, a network oscillation is expected to occur. However, in contrast to the continuous theta in the intact brain, theta-like oscillations in vitro consist of only a limited number of cycles (Konopacki et al., 1987; MacVicar and Tse, 1989; Traub et al., 1992; Van der Linden et al., 1999). A possible explanation for the short trains is that muscarinic receptor activation may attenuate the spread of collateral excitation. In support of this assertion, acetylcholine has been suggested to attenuate glutamate release from the recurrent and Schaffer collaterals (Hasselmo and Schnell, 1994). From the in vitro observations, it is tempting to conclude that the necessary and sufficient condition for the production of atropine-sensitive type of theta is a relatively intact CA3 recurrent collateral system and diffuse release of acetylcholine in the extracellular environment. However, when these conditions were created in vivo by grafting the fetal septal region into the subcortically denervated hippocampus, theta oscillation failed to emerge (Segal et al., 1985; Buzsáki et al., 1987) even though release of acetycholine from the graft reached physiological levels (Leanza et al., 1993). In addition, the magnitude of carbachol-induced synchrony in the hippocampal slice is several times larger than that observed in vivo (Traub et al., 1992). Despite these differences, the in vivo and in vitro experiments provide support for the existence of an intrinsic hippocampal theta oscillator. A broader implication of these observations is that in the behaving animal, the intrahippocampal (CA3) theta oscillator can change its frequency and phase relatively independently from the extrahippocampal (entorhinal) theta inputs (Kocsis et al., 1999). The phase differences, in turn, can have a profound effect on the timing of action potentials in the activated principal neurons.

The Involvement of GABAergic Interneurons in Theta Activity

Ample evidence supports the critical involvement of hippocampal interneurons in theta oscillations (Buzsáki et al., 1983). Hippocampal interneurons are the exclusive targets of the GABAergic septo-hippocampal projection (Freund and Antal, 1988) as well as the sole hippocampal output to the neurons of MS-DBB (Tóth et al., 1993). Thus, they are in a strategic position to amplify the hypothesized septo-hippocampal pacemaker connection. Nevertheless, the exact role of each of the numerous interneuron classes (Freund and Buzsáki, 1996) in this process has yet to be determined. In the behaving rat, the majority of CA1 interneurons discharge on the descending phase of theta in the pyramidal cells layer (ascending phase in the apical dendritic layers), and are assumed to be responsible for the increased γ power on this phase (Bragin et al., 1995). However, it is not known whether interneurons with different preferred theta phases represent different classes of cells or whether interneurons of the same class can discharge at different phases. At least three classes of interneurons deserve special attention: (1) basket and chandelier cells with perisomatic targets, (2) O-LM (oriens lacunosum-moleculare) and HIPP (hilar interneuron with perforant path axon projection) interneurons (Halasy and Somo-

gyi, 1993; Freund and Buzsáki, 1996), which specifically innervate the termination zones of entorhinal afferents, and (3) interneurons with feedback septal projection (Alonso and Kohler, 1982; Tóth et al., 1993).

Perisomatic inhibition plays an important role in timing the action potentials of principal cells within the theta cycle (Buzsáki et al., 1983). Basket and chandelier cells discharge rhythmically at γ frequency on the descending phase of the pyramidal layer theta and provide rhythmic hyperpolarization to the perisomatic region of pyramidal cells via $GABA_A$ receptor-mediated IPSPs (Artemenko, 1972; Fox, 1989; Leung and Yim, 1991; Soltesz and Deschénes, 1993; Ylinen et al., 1995; Cobb et al., 1995; Tóth et al., 1997). A functional consequence of such perisomatic shunting is periodic "isolation" of the somatic and dendritic compartments of pyramidal neurons at the time of maximum somatic inhibition (Figure 3A). Because the equilibrium potential of Cl^--mediated IPSPs is close to the resting membrane potential of the principal cells, the contribution of inhibition to the extracellular field depends on the state of the individual pyramidal cells. In the majority of pyramidal cells, the $GABA_A$ receptor-mediated transmembrane currents are very small because most pyramidal cells are silent during theta activity (Harris et al., 2000).Thus, the quantitative contribution of inhibition to the extracellular theta field has yet to be determined.

The role of $GABA_B$ receptors in theta oscillation is not clear. Activity of a single presynaptic interneuron rarely activates postsynaptic $GABA_B$ receptors (Buhl et al., 1994; Cobb et al., 1995). However, because at least 60% of putative basket cells discharge synchronously during the theta cycle (Csicsvari et al., 1999), activating more than half of the approximately 100 synapses on pyramidal cells (Megias et al., 2001), the amount of GABA released in the intact brain during theta may be sufficient to activate postsynaptic $GABA_B$ receptors (Dvorak-Carbone and Schuman, 1999; Scanziani, 2000). Nevertheless, the in vivo observation that intrasomatic theta has an amplitude minimum and phase reversal between -60 and -75 mV (Soltesz and Deschénes, 1993; Ylinen et al., 1995) indicates that the main ion responsible for the theta-related membrane hyperpolarization is Cl^- rather than K^+.

"Slow" $GABA_A$ receptors have also been implicated in theta oscillation. According to a recent model (Banks et al., 2000), an undisclosed subgroup of interneurons rhythmically inhibits the apical dendrites of both pyramidal cells and basket neurons via a slow type of $GABA_A$ receptor. In turn, rhythmic suppression of basket cells and, consequently, disinhibition of the somata of pyramidal cells are hypothesized to give rise to the extracellular theta field. An explicit prediction of this model is that basket cells and pyramidal neurons discharge on the opposite phases of theta, as observed under anesthesia (Ylinen et al., 1995; Buzsáki et al., 1983; Fox et al., 1986) and in vitro (Cobb et al., 1995). However, as discussed above, pyramidal cells and putative basket cells discharge on the same phase of the theta cycle in the freely behaving rat (Figure 3; Fox et al., 1986; Skaggs et al., 1996; Csicsvari et al., 1999).

Because current flow through the distal dendrites of principal cells is the most important event for the generation of extracellular theta currents, inhibitory regulation of these dendritic segments is critical in this process (Katona et al., 1999; Maccaferri et al., 2000). O-LM and HIPP interneurons specifically innervate the termination zones of entorhinal afferents on pyramidal cells and granule cells, respectively (Freund and Buzsáki, 1996). Since an important excitatory input to these interneurons is the local collaterals of CA1-CA3 pyramidal cells and granule cells (Sik et al., 1995, 1997; Blasco-Ibañez and Freund, 1995), the feedback dendritic inhibition can provide a "winner-take-all" mechanism and thereby prevent the discharge of weakly activated pyramidal neurons and granule cells. Assuming that O-LM and HIPP neurons fire on the same phase of theta waves as the input entorhinal cells, the outward inhibitory currents they bring about may effectively reduce the inward currents conveyed by the entorhinal afferents. The ratio of inhibitory versus excitatory terminals is 2- to 3-fold higher in str. lacunosum-moleculare as compared to the str. radiatum (Megias et al., 2001). On the other hand, selective reduction of distal dendritic inhibition in discharging pyramidal cells may allow for the backpropagation of action potentials from soma to dendrites (Spruston et al., 1995; Buzsáki et al., 1996; Tsubokawa and Ross, 1996). Temporal coordination of distal dendritic excitation and active spike backpropagation, in turn, may contribute to the theta frequency-triggered dendritic Ca^{2+} spikes (Figure 5).

A third group of cells that may be critically involved in the rhythm generation of theta oscillation is septally projecting interneurons (Alonso and Kohler, 1982; Tóth et al., 1993). This special group includes the "backprojection" or widely projecting class of interneurons (A.I. Gulyás et al., 2001, Soc. Neurosci., abstract). CA1 backprojection interneurons receive feedback excitation from CA1 pyramidal cells and innervate interneurons in the hilar area and CA3 region (Sik et al., 1994). Septally projecting interneurons discharge rhythmically during theta (G. Dragoi and G.B., unpublished observations). Although small in numbers, backprojection interneurons with septal collaterals are in a unique position to coordinate rhythmic discharge of large neuronal populations in both hippocampus and septum.

In addition to the above three groups, interneurons with intrinsic oscillatory properties in the theta frequency band may be also important for the maintenance of theta activity. Unfortunately, the exact anatomical identity of these interneurons is not known (Chapman and Lacaille, 1999). They may project back to the MS-DBB or may amplify rhythmic inputs from various sources and convey them to the principal cells and other interneuron partners. Finally, a small group of interneurons, termed "antitheta" cells, may also hold a key in understanding the emergence of theta oscillations because of their reciprocal firing relationship with all the other interneuron classes. Antitheta cells are virtually silent during theta oscillations, but fire rhythmically at 15–25 Hz in the absence of theta (Buzsáki et al., 1983; Mizumori et al., 1990). Their anatomical identity is unknown. Clarification of the role of various classes of interneurons in theta generation will require recording from identified interneurons in the awake animal. In addition, reversible "deletion" of the subclasses by molecular biological techniques will further aid in understanding their contribution.

Intrinsic Resonant Properties of Neurons Contribute to Theta Oscillations

Not only postsynaptic potentials but also intrinsic conductance changes of the neuronal membrane can contribute to the extracellularly recorded local field. Layer II stellate cells of the entorhinal cortex have been first described to possess voltage-dependent oscillatory properties in the theta frequency range (Alonso and Llinás, 1989). In these neurons, activation of a persistent Na^+ current may contribute to the membrane potential oscillation. Neurons of the MS-DBB are especially prone to voltage-dependent oscillations. Cholinergic cells display bursts of action potentials riding on low-threshold spikes recurring at a theta frequency. GABAergic neurons, on the other hand, display nonadapting clusters of spikes interspersed with rhythmic subthreshold membrane-potential oscillations (Alonso et al., 1996; Serafin et al., 1996). Voltage-dependent oscillations have also been described in the somata (Leung and Yim, 1991; Strata, 1998) and dendrites (Figure 5; Kamondi et al., 1998a) of hippocampal pyramidal cells. The presence of membrane resonance and subthreshold oscillations in hippocampal neurons suggests that they are not passive relays of incoming synaptic events, but rather participate in sculpting their final output, regulated by factors that control their resonant properties. The exact mechanisms of the intrinsic dendritic oscillation have yet to be revealed. One possibility is that high threshold dendritic Ca^{2+} currents amplify a subthreshold somatic oscillation. Another possibility is that activation of NMDA receptors is responsible for the rhythmic events (Peet et al., 1987). Furthermore, activation of the Ca^{2+} channels in distal apical dendrites is also facilitated by actively backpropagating action potentials (Kamondi et al., 1998a; Magee and Johnston, 1995). The type of Ca^{2+} channels involved in the amplification of theta oscillation is not known. Distal apical dendrites express a higher density of R- and T-type channels and a lower density of L- and N-type channels than the soma (Westenbroek et al., 1990; Magee and Johnston, 1995).

The role of other voltage-dependent conductancies has yet to be disclosed in the generation of theta waves. The transient K^+ current (I_A) is at a markedly higher density in the dendrites (Hoffman et al., 1997). The density of hyperpolarization-activated current (I_h) increases over 6-fold from soma to distal dendrites (Magee, 1999). Because I_h has its largest impact in the subthreshold range of membrane voltage, it may be particularly important in theta oscillation. During the theta cycle, the magnitude of the membrane potential can change considerably, therefore numerous voltage-dependent conductancies may be activated sequentially. In turn, activation of these conductancies can exert an important effect on the firing patterns of the principal cells.

Timing of Action Potentials within the Theta Cycle

A number of factors affect the precise timing of action potentials in depolarized pyramidal neurons. In the awake animal, REM sleep, and anesthesia, pyramidal neurons, on average, discharge on the negative phase of the theta cycle recorded from the CA1 pyramidal cell layer (Figure 3A). However, considerable variability exists in the phase of individual spikes (Figure 3B). Moreover, the phase fluctuation of spikes is not random and correlates with behavioral variables (O'Keefe and Recce, 1993). Let us first consider the consequences of simultaneous dendritic depolarization and somatic inhibition in a pyramidal neuron, the conditions that lead to maximum extracellular current flow. Threshold depolarization will induce an action potential on the peak of the depolarizing phase of the theta cycle (Figure 6). We assume that this weak but threshold dendritic depolarization is responsible for the single, sporadic spikes associated with the local positive peaks of pyramidal layer theta waves (Figure 3C). On the other hand, stronger dendritic excitation will bring the neuron to threshold earlier in the theta cycle. Because of the longer suprathreshold depolarization, more action potentials will be induced. However, the action potentials are asymmetrically distributed relative to the peak of intracellular depolarization (Figure 6), presumably because of Na^+ channel inactivation and/or because of the depolarization-induced activation of a slow K^+ current (Kamondi et al., 1998a). The overall result is a phase advancement of action potentials relative to the negative peak of the mean local field (i.e., the distributed "clock" theta signal).

Importantly, O'Keefe and Recce (1993) and Skaggs et al. (1996) have observed that the theta phase relationship of place cells varies systematically as the rat traverses the place field of the recorded unit. As the animal moves to the center of the field (as defined by the maximum discharge rate of the neuron), the first action potential and the median of action potentials can advance at least 180° during successive theta cycles (O'Keefe and Recce, 1993; Skaggs et al., 1996). Computational models have offered several potential solutions for the phase precession of action potentials (Tsodyks et al., 1996; Jensen and Lisman, 1996; Wallenstein and Hasselmo, 1997). The potential importance of the spike-phase precession phenomenon is that it may be taken as an indication that neurons encode information by timing instead of or in addition to firing rate (König et al., 1996; Hopfield, 1995; Buzsáki and Chrobak, 1995; Lisman and Idiart, 1995). Because the exact timing of spikes within the theta cycle varies systematically when the rat crosses the place field of the recorded neuron, it was suggested that place is encoded by the spike-theta phase relationship (Skaggs et al., 1996; Jensen and Lisman, 2000). However, since the spatial position of the rat can be also deduced from the firing rates of hippocampal pyramidal neurons (O'Keefe and Nadel, 1978; Wilson and McNaughton, 1993), an important issue is whether firing rate increase and phase advancement of spikes are produced by the same or different mechanisms. If a single mechanism is responsible for both changes, then space or other behavioral variables (Eichenbaum, 2000) may be redundantly coded by both discharge frequency and timing of the action potentials. On the other hand, if firing rate and spike-phase advancement can be dissociated experimentally, it suggests that these different mechanisms can code different stimulus dimensions or representations (Hirase et al., 2000).

Large and systematic phase shifts can be brought about by the interference of two oscillators with slightly different frequencies (O'Keefe and Recce, 1993; Jensen

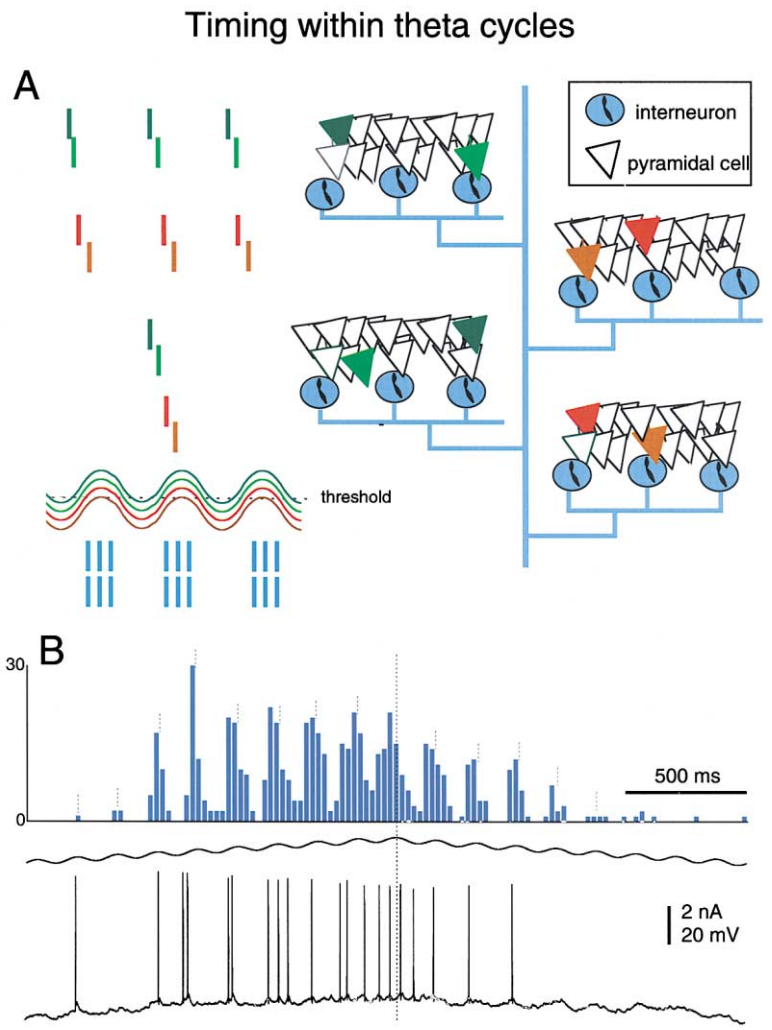

Figure 6. Oscillation of Inhibitory Networks Provides a Clock Signal for Timing of Action Potentials of Pyramidal Neurons

(A) The interconnected inhibitory interneurons rhythmically hyperpolarize spatially distant pyramidal cells. The timing of the action potentials is determined by the magnitude of the excitatory drive to the pyramidal cells: more strongly driven neurons will discharge earlier during the theta cycle. Interneurons discharge regularly at each theta cycle (light blue ticks). (B) Phase advancement of action potentials in the anesthetized rat. Theta oscillation was mimicked by sinusoid somatic current injection (0.05 nA). Place field activation in the awake animal was mimicked by adding a 2 s triangular waveform (gray trace). Bottom: a single trial. Histogram : average of 50 events. Dotted lines: peaks of the sinus oscillation. Note that most action potentials occur on the rising phase of oscillation and at progressively earlier phases upon increasing levels of depolarization. Note also the asymmetric distribution of spikes on the depolarizing and repolarizing parts of the ramp, resembling the asymmetric nature of place fields (Mehta et al., 2000). Reprinted from Buzsáki and Chrobak (1995); Parts (B) and (D), A. Henze and G.B., unpublished data.

and Lisman, 1996). As discussed earlier, the extrahippocampal (entorhinal) and intrahippocampal (CA3) theta oscillators can be relatively independent. If the average field theta is determined primarily by the entorhinal input but place-related discharge requires the CA3 input as well, then a faster CA3 theta oscillator can bring about a full theta cycle spike advancement. The observation that CA3 and CA1 pyramidal neurons discharge on the same phase of theta (Fox et al., 1986; J. Csicsvari and G.B., unpublished data) provides support for the hypothesis that the CA3 input is the major driving source of the discharging CA1 pyramidal neurons.

The activity-dependent theta phase advancement of spike may shed light on the controversy between field measurements of theta waves and the timing of spikes during the theta cycle. The entorhinal input appears to be relatively sustained (Brankack et al., 1993) because layer III neurons are active over very large spatial areas (Barnes et al., 1990). Although most pyramidal neurons are silent during theta (Harris et al., 2000), the voltage fluctuation in their membrane, nevertheless, also contributes to theta. The maximum dendritic depolarization corresponds to the negative peak of theta waves present in str. lacunosum-moleculare, mirrored by the positive peak of theta waves in str. oriens/pyramidale (Figures 1 and 4). It is possible that the low-frequency single spikes that occur on the positive peaks of the locally derived theta (Figure 3B) are brought about by the entorhinal input. On the other hand, stronger activation may require the cooperation of entorhinal and CA3 inputs and the more strongly activated neurons will discharge earlier in phase. Place cells discharge fastest in the center of the field that corresponds to approximately 180° of phase advancement (Skaggs et al., 1996). Because <3% of CA1 pyramidal cells are active during the theta cycle (Csicsvari et al., 1998) and because the majority of spikes are emitted within the place field, the mean spike-theta phase relationship of the cell population (Figure 3A) is therefore strongly biased by the phase-advanced place cells. The slowly discharging majority, in fact, may have an opposite phase relationship (Figure 3C). These observations suggest that while most neurons contribute to the generation of field theta, it is the strongly active minority that is responsible for the empirically derived spike-phase relationship (Figure 3A). In turn, this relationship could resolve the controversy between results derived from CSD unit recording studies regarding the relationship between afferent exci-

tation and the theta cycle-related discharges of CA1 pyramidal cells.

Overall, these considerations suggest that modeling the generation of the extracellular theta field with a single "average" pyramidal cell (Figure 2) is not adequate. The timing of the action potentials within the theta cycle depends on the activity level of pyramidal cell and other hitherto unknown factors. We suggest that the behavior-dependent variability of spike timing may explain the discrepancy between the empirical observations (Figure 3) and the expected timing of the spikes on the basis of extracellular theta sinks and sources (Figure 4).

Hippocampal Plasticity during Theta Oscillations

Although indirect, several observations suggest the possible involvement of theta oscillations in synaptic plasticity. A number of in vitro and in vivo studies have reported that induction of long-term potentiation (LTP) is optimal when the time interval between stimuli is approximately 200 ms (Larson and Lynch, 1986; Greenstein et al., 1988). Rhythmic stimulation at theta frequency is not needed though and two high-frequency bursts are sufficient. When two identical bursts are applied repeatedly to two different inputs at 200 ms intervals, only the synapses activated by the second burst show potentiation (Larson and Lynch, 1986). In fact, the priming stimulus can be a single pulse (Rose and Dunwiddie, 1986). The mechanism underlying the priming effect is largely unknown. It may block a normally present outward current (e.g., I_A; Hoffman et al., 1997) or activate an NMDA receptor-mediated inward current (Larson and Lynch, 1986). Alternatively, the priming stimulus-induced hyperpolarization may activate I_h conductance or remove the inactivation of T-type of Ca^{2+} channels followed by a rebound depolarization after 100–200 ms (Cobb et al., 1995). A third possibility is that GABA released from terminals or cannabiods released from the discharging neuron in response to the first pulse may block further GABA release by the subsequent train (Wilson and Nicoll, 2001; Hájos et al., 2000). Thus, the priming stimulus prepares the network so that all neurons will be optimally depolarized by the burst stimulus. However, it is not clear yet how these postulated events relate to the conductance changes present during the in vivo theta cycle.

The priming stimulus may be substituted by a previous theta cycle in oscillating hippocampal networks. When a single tetanic train (four pulses at 100 Hz) is delivered during the positive peak of carbachol-induced theta-like waves in CA1 str. radiatum, LTP occurs (Huerta and Lisman, 1996). Importantly, a single burst (200 Hz) of five pulses was also sufficient for the potentiation of the Schaffer collateral response in the anesthetized rat (Höschler et al., 1997). Because the positive peak of str. radiatum theta (i.e., negative phase of theta in the pyramidal layer) corresponds to the highest probability of pyramidal cell discharge (Fox et al., 1986; Buzsáki et al., 1983), the phase-locked discharge of neurons may substitute for the priming pulse. Similar observations were made also in the dentate gyrus, although the relationship between the phase of theta and neuronal excitability is less clear in this region (Pavlides et al., 1988).

Why is potentiation so efficient during theta? Various factors that act in concert during the theta cycle may be responsible. When theta-like oscillation is induced in the slice by carbachol, part of the effect may be explained by the drug's blocking effect of $GABA_A$ receptors (MacVicar and Tse, 1989). Importantly, carbachol has been shown to facilitate the somadendritic propagation of action potentials through activation of muscarinic receptors (Tsubokawa and Ross, 1997). Backpropagating spikes into the synaptically activated dendritic segments, in turn, have been shown to be important for the enhancement of synaptic weights (Magee and Johnston, 1995). LTP may occur because large amplitude fast spikes in dendrites can serve as a trigger of Ca^{2+} spikes (Kamondi et al., 1998b). In turn, the large depolarization associated with Ca^{2+} spikes can enable NMDA receptors. In vivo, theta-associated somatic hyperpolarization may provide silent periods necessary for the occurrence of complex spike bursts (Harris et al., 2001), a condition necessary for synaptic potentiation (Paulsen and Sejnowski, 2000). Thus, theta oscillation may provide a mechanism for bringing together in time afferent-induced depolarization of pyramidal cell dendrites and dendritic invasion of fast spikes, the key elements for the induction of synaptic plasticity. Assuming that these observations in vitro and in the anesthetized rat can be generalized to the brains of behaving animals, we can assign a specific physiological role to the intrahippocampal trisynaptic pathway. During theta oscillation, repeated pairing of distal dendritic depolarization by the entorhinal input and the trisynaptically activated CA3 recurrent/Schaffer collaterals to CA3 and CA1 pyramidal cells can result in synaptic modification of the intrahippocampal associational pathways. As a result, these modified pathways will give rise to endogenous population patterns in the absence of the entorhinal inputs during non-theta activity. Reactivation of the same synapses can further strengthen their efficacy (Buzsáki, 1989). The synaptic modification, brought about by the two-step process, in turn, will allow memory retrieval.

When repeated trains are delivered on the negative peak of the theta recorded in the str. radiatum, the previously potentiated pathway becomes depotentiated (Huerta and Lisman, 1996; Höschler et al., 1997). Therefore, timing of the dendritic excitatory inputs during the theta cycle is critical for the strengthening and weakening of synapses. As discussed earlier, action potentials occur on progressively earlier phases of the theta cycle as the rat traverses the place field of the recorded unit (O'Keefe and Recce, 1993; Skaggs et al., 1996). Thus, if theta phase-dependent potentiation and depotentiation also hold in the intact brain (Höschler et al., 1997), one might expect that the synapses which bring about place-related activity undergo both potentiation and depotentiation every time the rat visits the place field of the neuron. Alternatively, pyramidal cells representing the same part of the environment may recurrently discharge their common basket and chandelier neurons (Csicsvari et al., 1998); thus dendritic depolarization and somatic hyperpolarization will still occur in phase for this subnet. As discussed in the previous section, this hypothesis assumes that the activated subnet of pyramidal cells and interneurons (i.e., a cell assembly) can "step out" from the theta cycle represented by the nonspiking or slowly discharging population (Marshall et al., 2002). We hypothesize that an important function of the theta

oscillation is to assemble and segregate neuronal groups. The segregated assembles then can "wire together" and exert a differential effect on their downstream neurons.

Significance of Theta Oscillations and Future Directions

Brain waves reflect the collective behavior of neurons and provide insight into the fast periodic changes of the network. Theta oscillations reliably correlate with a variety of behaviors. The theta versus non-theta dichotomy objectively groups behaviors into preparatory versus consummatory classes (Sherrington, 1897).

Field theta waves and phase-locked discharge of neurons are observed in a large number of brain structures. These structures are members of the anatomically defined limbic system (Broca, 1878). Thus, theta oscillation can be used to functionally determine parts of an anatomical macrosystem. Consequently, "limbic theta oscillation" is a more appropriate term than hippocampal theta. A theta cycle may be considered as an information quantum, allowing the exchange of information among the linked members in a phase-locked manner. This discontiguous (cyclic) mode of operation may be a unique solution to temporarily segregate and link neuronal assemblies to perform various operations. From this perspective, theta oscillation is a computational process that brings together activity of sensory- and/or memory-activated neurons in time, thereby affecting behavioral output and plasticity. Examples of these operations include phase reset of the theta cycle by sensory stimulation (Buzsáki et al., 1979; Givens, 1996; Tesche and Karhu, 2000), theta phase locking of motor activity (Buño and Velluti, 1977; Semba and Komisaruk, 1978), memory encoding and retrieval (Hasselmo et al., 2002), and synaptic potentiation of sequentially activated place neurons (Mehta et al., 2000).

Because neurons in the entorhinal cortex, hippocampus, and septum are endowed with numerous voltage-dependent channels and intrinsic resonant properties, sequential activation of voltage-dependent conductancies during the theta cycle may set constraints for excitability and plasticity. For example, artificial stimulation of any hippocampal pathway results in either accommodation or augmentation of the response. In contrast, physiological activation of the same inputs during theta activity may maintain stable firing patterns for prolonged periods (Czurkó et al., 1999). Exploration of the significance of the cyclic conductance changes in future experiments is a necessary step to provide an insight into the physiological role of theta. During theta oscillation, the dendrites of pyramidal cells can depolarize to −45 mV, thus potentially activating/inactivating a host of voltage-gated channels. The sequential activation and inactivation of the numerous conductancies in pyramidal cells and interneurons may offer clues to the physiological significance of theta oscillation in synaptic transmission and plasticity. These issues can be explored in vitro using sinusoid stimulation of the soma and dendrites at theta frequency (Kamondi et al., 1998a; Magee, 2001).

Although the extracellularly recorded field reflects the summed activity of membrane currents over a relatively large volume of neurons, active neurons may contribute disproportionally more to the field than nonspiking cells. In future studies, large-scale recordings spanning across different hippocampal regions should be used to reveal whether subnets of active neurons behave differently from the "average" population. The coherent oscillations of cell assemblies during theta provide an ideal mechanism for temporal coding and decoding (Lisman and Idiart, 1995; Wallenstein and Hasselmo, 1997). Theta phase precession of action potentials in activated neurons supports the idea that phase coding is exploited by the hippocampus and associated structures. However, further research is required to determine whether phase coding and rate coding are redundant or whether they are used to register different types of information. On the basis of the efficient and tunable pyramidal cell-interneuron feedback (Markram et al., 1998; Marshall et al., 2002), we hypothesize that this mechanism allows active pyramidal cells and their common interneurons to beat at slightly different frequency and phase than the "master clock" rhythm of theta. As a result, the phase differences can segregate assemblies of neurons that are assigned to different representations.

Addressing many of these issues requires the analytical power of in vitro preparations. The dynamic relationship between pyramidal cell discharge and the postsynaptic response of the various interneuron classes should be worked out in detail. On the other hand, a coordinated effort is needed to compare the physiological relevance of the in vitro observations to the intact brain. In addition to physiological experiments, several topics could benefit from computational models. For example, modeling extracellular current flow using networks of neurons may yield insights into the relative contribution of spiking and nonspiking neurons to local field potentials. Genetic modification of channels and receptors can confront the relationship between single cell and network properties. Theta oscillation is a physiologically relevant phenotype that provides a sensitive assay for the measurement of ensemble properties of neurons.

Most known disease-related impairments of the hippocampus are associated with structural damage of its neurons. Because theta oscillation is a major operational mode of the hippocampus, it is expected that functional impairment of its oscillatory mode may be equally detrimental to mental health. Noninvasive, clinically applicable methods (Tesche and Karhu, 2000) are now available to examine whether and how this population pattern is affected in schizophrenia, epilepsy, Alzheimer's disease, and other diseases.

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References

Adey, W.R. (1967). Hippocampal states and functional relations with corticosubcortical systems in attention and learning. Prog. Brain Res. *27*, 228–245.

Alonso, A., and Garcia-Austt, E. (1987). Neuronal sources of theta rhythm in the entohrinal cortex of the rat. I. Laminar distribution of theta field potentials. Exp. Brain Res. *67*, 493–501.

Alonso, A., and Kohler, C. (1982). Evidence for separate projections of hippocampal pyramidal and non-pyramidal neurons to different parts of the septum in the rat brain. Neurosci. Lett. *31*, 209–214.

Alonso, A., and Llinás, R.R. (1989). Subthreshold Na+-dependent theta-like rhythmicity in stellate cells of entorhinal cortex layer II. Nature *342*, 175–177.

Alonso, A., Khateb, A., Fort, P., Jones, B.E., and Muhlethaler, M. (1996). Differential oscillatory properties of cholinergic and noncholinergic nucleus neurons in guinea pig brain slice. J. Neurosci. *8*, 169–182.

Amaral, D.G., and Witter, M.P. (1989). The three-dimensional organization of the hippocampal formation: a review of anatomical data. Neuroscience *31*, 571–591.

Arnolds, D.E., Lopes da Silva, F.H., Aitink, J.W., Kamp, A., and Boeijinga, P. (1980). The spectral properties of hippocampal EEG related to behaviour in man. Electroencephalogr. Clin. Neurophysiol. *50*, 324–328.

Artemenko, D.P. (1972). Role of hippocampal neurons in theta-wave generation. Neurophysiologia *4*, 409–415.

Banks, M.I., White, J.A., and Pearce, R.A. (2000). Interactions between distinct GABA(A) circuits in hippocampus. Neuron *25*, 449–457.

Barnes, C.A., McNaughton, B.L., Mizumori, S.J., Leonard, B.W., and Lin, L.H. (1990). Comparison of spatial and temporal characteristics of neuronal activity in sequential stages of hippocampal processing. Prog. Brain Res. *83*, 287–300.

Bland, B.H. (1986). Physiology and pharmacology of hippocampal formation theta rhythms. Prog. Neurobiol. *26*, 1–54.

Bland, B.H., Andersen, P., and Ganes, T. (1975). Two generators of hippocampal theta activity in rabbits. Exp. Brain Res. *94*, 199–218.

Bland, B.H., Colom, L.V., Konopacki, J., and Roth, S.H. (1988). Intracellular records of carbachol-induced theta rhythm in hippocampal slices. Brain Res. *447*, 364–368.

Blasco-Ibañez, J.M., and Freund, T.F. (1995). Synaptic input of horizontal interneurons in stratum oriens of the hippocampal CA1 subfield: structural basis of feed-back activation. Eur. J. Neurosci. *7*, 2170–2180.

Bódizs, R., Kántor, S., Szücs, A., Eröss, L., and Halász, P. (2001). Rhythmic hippocampal slow oscillation characterizes REM sleep in humans. Hippocampus *11*, 747–753.

Borhegyi, Z., and Freund, T.F. (1998). Dual projection from the medial septum to the supramammillary nucleus in the rat. Brain Res. Bull. *46*, 453–459.

Borisyuk, R., and Hoppensteadt, F. (1999). Oscillatory models of the hippocampus: a study of spatio-temporal patterns of neural activity. Biol. Cybern. *81*, 359–371.

Bragin, A., Jando, G., Nádasdy, Z., Hetke, J., Wise, K., and Buzsáki, G. (1995). Gamma frequency (40–100 Hz) patterns in the hippocampus of the behaving rat. J. Neurosci. *15*, 47–60.

Brankack, J., Stewart, M., and Fox, S.E. (1993). Current source density analysis of the hippocampal theta rhythm: associated sustained potentials and candidate synaptic generators. Brain Res. *615*, 310–327.

Brazhnik, E.S., and Fox, S.E. (1999). Action potentials and relations to the theta rhythm of medial septal neurons *in vivo.* Exp. Brain Res. *127*, 244–258.

Broca, P. (1878). Anatomie compareé circonvolutions cérébrales; le grand lobe limbique et la scissure limbiquie dans la série des mammiféres. Rev. Antropol. Series 2. *1*, 385–498.

Buhl, E.H., Halasy, K., and Somogyi, P. (1994). Diverse sources of hippocampal unitary inhibitory postsynaptic potentials and the number of synaptic release sites. Nature *368*, 823–828.

Bullock, T.H., Buzsáki, G., and McClune, M.C. (1990). Coherence of compound field potentials reveals discontinuities in the CA1-subiculum of the hippocampus in freely-moving rats. Neuroscience *38*, 609–619.

Buño, W., Jr., and Velluti, J.C. (1977). Relationships of hippocampal theta cycles with bar pressing during self-stimulation. Physiol. Behav. *19*, 615–621.

Buzsáki, G. (1989). Two-stage model of memory trace formation: a role for "noisy" brain states. Neuroscience *31*, 551–570.

Buzsáki, G., and Chrobak, J.J. (1995). Temporal structure in spatially organized neuronal ensembles: a role for interneuronal networks. Curr. Opin. Neurobiol. *5*, 504–510.

Buzsáki, G., Grastyán, E., Tveritskaya, I.N., and Czopf, J. (1979). Hippocampal evoked potentials and EEG changes during classical conditioning in the rat. Electroencephalogr. Clin. Neurophysiol. *47*, 64–74.

Buzsáki, G., Leung, L., and Vanderwolf, C.H. (1983). Cellular bases of hippocampal EEG in the behaving rat. Brain Res. Bran Res. Rev. *6*, 139–171.

Buzsáki, G., Czopf, J., Kondakor, I., and Kellenyi, L. (1986). Laminar distribution of hippocampal rhythmic slow activity (RSA) in the behaving rat: Current source density analysis, effects of urethane and atropine. Brain Res. *365*, 125–137.

Buzsáki, G., Gage, F.H., Kellenyi, L., and Bjorklund, A. (1987). Behavior dependence of the electrical activity of intracerebrally transplanted fetal hippocampus. Brain Res. *400*, 334–347.

Buzsáki, G., Freund, T.F., Bayardo, F., Leon, A., and Somogyi, P. (1990). Ischemia-induced changes in the electrical activity of the hippocampus. Exp. Brain Res. *78*, 268–278.

Buzsáki, G., Bragin, A., Chrobak, J.J., Nádasdy, Z., Sik, A., Hsu, M., and Ylinen, A. (1994). Oscillatory and intermittent synchrony in the hippocampus: relevance to memory trace formation. In Temporal Coding in the Brain, G. Buzsáki, R. Llinás, W. Singer, A. Bethoz, and Y. Christen, eds. (Berlin: Springer-Verlag), pp.145–172.

Buzsáki, G., Penttonen, M., Nádasdy, Z., and Bragin, A. (1996). Pattern and inhibition-dependent invasion of pyramidal cell dendrites by fast spikes in the hippocampus *in vivo.* Proc. Natl. Acad. Sci. USA *93*, 9921–9925.

Chapman, C.A., and Lacaille, J.C. (1999). Cholinergic induction of theta-frequency oscillations in hippocampal inhibitory interneurons and pacing of pyramidal cell firing. J. Neurosci. *19*, 8637–8645.

Cobb, S.R., Buhl, E.H., Halasy, K., Paulsen, O., and Somogyi, P. (1995). Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. Nature *378*, 75–98.

Cole, A.E., and Nicoll, R.A. (1983). Acetylcholine mediates a slow synaptic potential in hippocampal pyramidal cells. Science *221*, 1299–1301.

Csicsvari, J., Hirase, H., Czurkó, A., and Buzsáki, G. (1998). Reliability and state dependence of pyramidal-interneuron synapses in the hippocampus: an ensemble approach in the behaving rat. Neuron *21*, 179–189.

Csicsvari, J., Hirase, H., Czurkó, A., Mamiya, A., and Buzsáki, G. (1999). Oscillatory coupling of hippocampal pyramidal cells and interneurons in the behaving rat. J. Neurosci. *19*, 274–287.

Czurkó, A., Hirase, H., Csicsvari, J., and Buzsáki, G. (1999). Sustained activation of hippocampal pyramidal cells by "space clamping" in a running wheel. Eur. J. Neurosci. *11*, 344–353.

Denham, M.J., and Borisyuk, R.M. (2000). A model of theta rhythm production in the septal-hippocampal system and its modulation by ascending brain stem pathways. Hippocampus *10*, 698–716.

Dvorak-Carbone, H., and Schuman, E.M. (1999). Patterned activity in stratum lacunosum moleculare inhibits CA1 pyramidal firing. Neurophysiol. *82*, 3213–3222.

Eichenbaum, H. (2000). Hippocampus: mapping or memory? Curr. Biol. *10*, R785–R797.

Fellous, J.M., and Sejnowski, T.J. (2000). Cholinergic induction of oscillations in the hippocampal slice in the slow (0.5–2 Hz), theta (5–12 Hz), and gamma (35–70 Hz) bands. Hippocampus *10*, 187–197.

Fischer, Y., Gahwiler, B.H., and Thompson, S.M. (1999). Activation of intrinsic hippocampal theta oscillations by acetylcholine in rat septo-hippocampal co-cultures. J. Physiol. (Lond.) *519*, 405–413.

Fox, S.E. (1989). Membrane potential and impedance changes in

hippocampal pyramidal cells during theta rhythm. Exp. Brain Res. *77*, 283–294.

Fox, S.E., Wolfson, S., and Ranck, J.B., Jr. (1986). Hippocampal theta rhythm and the firing of neurons in walking and urethane anesthetized rats. Exp. Brain Res. *62*, 495–508.

Freund, T.F., and Antal, M. (1988). GABA-containing neurons in the septum control inhibitory interneurons in the hippocampus. Nature *336*, 170–173.

Freund, T.F., and Buzsáki, G. (1996). Interneurons of the hippocampus. Hippocampus *6*, 347–470.

Givens, B. (1996). Stimulus-evoked resetting of the dentate theta rhythm: relation to working memory. Neuroreport *8*, 159–163.

Grastyán, E., Lissák, K., Madarász, I., and Donhoffer, H. (1959). Hippocampal electrical activity during the development of conditioned reflexes. Electroencephal. Clin. Neurophysiol. *11*, 409–430.

Greenstein, Y.J., Pavlides, C., and Winson, J. (1988). Long-term potentiation in the dentate gyrus is preferentially induced at theta periodicity. Brain Res. *438*, 331–334.

Hájos, N., Papp, E.C., Acsády, L., Levey, A.I., and Freund, T.F. (1998). Distinct interneuron types express m2 muscarinic receptor immunoreactivity their dendrites or axon terminals in the hippocampus. Neuroscience *82*, 355–376.

Hájos, N., Katona, I., Naiem, S.S., MacKie, K., Ledent, C., Mody, I., and Freund, T.F. (2000). Cannabinoids inhibit hippocampal GABAergic transmission and network oscillations. Eur. J. Neurosci. *12*, 3239–3249.

Halasy, K., and Somogyi, P. (1993). Subdivisions in the multiple GABAergic innervation of granule cells in the dentate gyrus of the rat hippocampus. J. Neurosci. *5*, 411–429.

Harris, K., Henze, D.A., Hirase, H., Csicsvari, J., and Buzsáki, G. (2000). The accuracy of tetrode spike separation as determined by simultaneous intracellular and extracellular measurements. J. Neurophysiol. *84*, 401–414.

Harris, K., Hirase, H., Leinekugel, X., Henze, D.A., and Buzsáki, G. (2001). Temporal interaction between single spikes and complex spike bursts in hippocampal pyramidal cells. Neuron *32*, 141–149.

Hasselmo, M.E., and Fehlau, B.P. (2001). Differences in time course of cholinergic and GABAergic modulation of excitatory synaptic potentials in rat hippocampal slice preparations. J. Neurophysiol. *86*, 1792–1802.

Hasselmo, M.E., and Schnell, E. (1994). Laminar selectivity of the cholinergic suppression of synaptic transmission in rat hippocampal region CA1: computational modeling and brain slice physiology. J. Neurosci. *14*, 3898–3914.

Hasselmo, M.E., Bodelon, C., and Wyble, B.P. (2002). A proposed function for hippocampal theta rhythm: Separate phases of encoding and retrieval enhance reversal of prior learning. Neural Comput., in press.

Häusser, M., Spruston, N., and Stuart, G.J. (2000). Diversity and dynamics of dendritic signaling. Science *290*, 739–744.

Henze, D.A., Urban, N.N., and Barrionuevo, G. (2000). The multifarious hippocampal mossy fiber pathway: a review. Neuroscience *98*, 407–427.

Hirase, H., Czurkó, A., Csicsvari, J., and Buzsáki, G. (2000). Firing rate and theta-phase coding by hippocampal pyramidal neurons during "space clamping." Eur. J. Neurosci. *11*, 4373–4380.

Hoffman, D.A., Magee, J.C., Colbert, C.M., and Johnston, D. (1997). K^+ channel regulation of signal propagation in dendrites of hippocampal pyramidal neurons. Nature *387*, 869–875.

Holsheimer, J., Boer, J., Lopes da Silva, F., and Van Rotterdam, A. (1982). The double dipole model of theta rhythm generation: simulation of laminar field potential profiles in dorsal hippocampus of rat. Brain Res. *235*, 31–50.

Hopfield, J.J. (1995). Pattern recognition computation using action potential timing for stimulus representation. Nature *376*, 33–36.

Horvath, Z., Kamondi, A., Czopf, J., Bliss, T.V.P., and Buzsáki, G. (1988). NMDA receptors may be involved in generation of hippocampal theta rhythm. In Synaptic Plasticity in the Hippocampus, H.L. Haas and G. Buzsáki, eds. (Berlin: Springer-Verlag), p. 45.

Höschler, C., Anwyl, R., and Rowan, M.J. (1997). Stimulation on the positive phase of hippocampal theta rhythm induces long-term potentiation that can be depotentiated by stimulation on the negative phase in area CA1 *in vivo*. J. Neurosci. *17*, 6470–6477.

Huerta, P.T., and Lisman, J.E. (1996). Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 *in vitro*. Neuron *15*, 1053–1063.

Jensen, O., and Lisman, J.E. (1996). Hippocampal CA3 region predicts memory sequences: accounting for the phase precession of place cells. Learn. Mem. *3*, 279–287.

Jensen, O., and Lisman, J.E. (2000). Position reconstruction from an ensemble of hippocampal place cells: contribution of theta phase coding. J. Neurophysiol. *83*, 2602–2609.

Ji, D.Y., and Dani, J.A. (2000). Inhibition and disinhibition of pyramidal neurons by activation of nicotinic receptors on hippocampal interneurons. J. Neurophysiol. *83*, 2682–2690.

Jouvet, M. (1969). Biogenic amines and the states of sleep. Science *163*, 32–41.

Kahana, M.J., Sekuler, R., Caplan, J.B., Kirschen, M., and Madsen, J.R. (1999). Human theta oscillations exhibit task dependence during virtual maze. J. Neurosci. *399*, 781–784.

Kamondi, A., Acsády, L., Wang, X.-J., and Buzsáki, G. (1998a). Theta oscillations in somata and dendrites of hippocampal pyramidal cells in vivo: activity dependent phase-precession of action potentials. Hippocampus *8*, 244–261.

Kamondi, A., Acsády, L., and Buzsáki, G. (1998b). Dendritic spikes are enhanced by cooperative network activity in the intact hippocampus. J. Neurosci. *18*, 3919–3928.

Kandel, E.R., and Squire, L.R. (2000). Neuroscience: breaking down scientific barriers to the study of brain and mind. Science *290*, 1113–1120.

Katona, I., Acsády, L., and Freund, T.F. (1999). Postsynaptic targets of somatostatin-immunoreactive interneurons in the rat hippocampus. Neuroscience *88*, 37–55.

Kentros, C., Hargreaves, E., Hawkins, R.D., Kandel, E.R., Shapiro, M., and Muller, R.V. (1998). Abolition of long-term stability of new hippocampal place cell maps by NMDA receptor blockade. Science *280*, 2121–2126.

King, C., Recce, M., and O'Keefe, J. (1998). The rhythmicity of cells of the medial septum/diagonal band of Broca in the freely moving rat: relationships with behaviour and hippocampal theta. Eur. J. Neurosci. *10*, 464–477.

Kocsis, B., Bragin, A., and Buzsáki, G. (1999). Interdependence of multiple theta generators in the hippocampus: a partial coherence analysis. J. Neurosci. *19*, 6200–6212.

König, P., Engel, A.K., and Singer, W. (1996). Integrator or coincidence detector? The role of the cortical neuron revisited. Trends Neurosci. *19*, 130–137.

Konopacki, J., MacIver, M.B., Bland, B.H., and Roth, S.H. (1987). Theta in hippocampal slices: relation to synaptic responses of dentate neurons. Brain Res. Bull. *18*, 25–27.

Kovalchuk, Y., Eilers, J., Lisman, J., and Konnerth, A. (2000). NMDA receptor-mediated subthreshold Ca(2+) signals in spines of hippocampal neurons. J. Neurosci. *20*, 1791–1799.

Kramis, R., Vanderwolf, C.H., and Bland, B.H. (1975). Two types of hippocampal rhythmical slow activity in both the rabbit and the rat: relations to behavior and effects of atropine, diethyl ether, urethane, and pentobarbital. Exp. Neurol. *49*, 58–85.

Larson, J., and Lynch, G. (1986). Induction of synaptic potentiation in hippocampus by patterned stimulation two events. Science *232*, 985–988.

Leanza, G., Nilsson, O.G., and Bjorklund, A. (1993). Functional activity of intrahippocampal septal grafts is regulated by host afferents as studied by microdialysis of acetylcholine. Brain Res. *618*, 47–56.

Lee, M.G., Chrobak, J.J., Sik, A., Wiley, R.G., and Buzsáki, G. (1994). Hippocampal theta following selective lesion of the septal cholinergic system. Neuroscience *62*, 1033–1047.

Leranth, C., Carpi, D., Buzsáki, G., and Kiss, J. (1999). The entorhino-septo-supramammillary nucleus connection in the rat: morphologi-

cal basis of a feedback mechanism regulating hippocampal theta rhythm. Neuroscience *88*, 701–718.

Leung, L.S. (1984). Model of gradual phase shift of theta rhythm in the rat. J. Neurophysiol. *52*, 1051–1065.

Leung, L.W., and Borst, J.G. (1987). Electrical activity of the cingulate cortex. I. Generating mechanisms and relations to behavior. Brain Res. *407*, 68–80.

Leung, L.S., and Yim, C.Y. (1986). Intracellular records of theta rhythm in hippocampal CA1 cells of the rat. Brain Res. *367*, 323–327.

Leung, L.S., and Yim, C.Y. (1991). Intrinsic membrane potential oscillations in hippocampal neurons *in vitro.* Brain Res. *553*, 261–274.

Lisman, J.E., and Idiart, M.A. (1995). Storage of 7 $\pm$2 short-term memories in oscillatory subcycles. Science *267*, 1512–1515.

Llinás, R.R. (1988). The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. Science *242*, 1654–1664.

Lopes da Silva, F.H., Witter, M., Boeijinga, P.H., and Lohman, A. (1990). Anatomic organization and physiology of the limbic cortex. Physiol. Rev. *70*, 453–511.

Maccaferri, G., Roberts, J.D., Szücs, P., Cottingham, C.A., and Somogyi, P. (2000). Cell surface domain specific postsynaptic currents evoked by identified GABAergic neurones in rat hippocampus in vitro. J. Physiol. *524*, 91–116.

MacVicar, B.A., and Tse, F.W. (1989). Local neuronal circuitry underlying cholinergic rhythmical slow activity in CA3 area of rat hippocampal slices. J. Physiol. *417*, 197–212.

Madison, D.V., Lancaster, B., and Nicoll, R.A. (1987). Voltage clamp analysis of cholinergic action in the hippocampus. Neuroscience *7*, 733–741.

Magee, J.C. (1999). Dendritic Ih normalizes temporal summation in hippocampal CA1 neurons. Nat. Neurosci. *2*, 508–514.

Magee, J.C. (2001). Dendritic mechanisms of phase precession in hippocampal CA1 pyramidal neurons. J. Neurophysiol. *86*, 528–532.

Magee, J.C., and Johnston, D. (1995). Synaptic activation of voltage-gated channels in the dendrites of hippocampal pyramidal neurons. Science *268*, 301–304.

Markram, H., Gupta, A., Uziel, A., Wang, Y., and Tsodyks, M. (1998). Information processing with frequency-dependent synaptic connections. Neurobiol. Learn. Mem. *70*, 101–112.

Marshall, L., Hirase, H., Leinekugel, X., Dragoi, G., Henze, D.A., and Buzsáki, G. (2002). Hippocampal pyramidal cell-interneuron spike transmission is reliable and responsible for place modulation of interneuron discharge. J. Neurosci. *22*, RC197.

McMahon, L.L., Williams, J.H., and Kauer, J.A. (1998). Functionally distinct groups of interneurons identified during rhythmic oscillations in hippocampus in vitro. J. Neurosci. *18*, 5640–5651.

Megias, M., Emri, Z., Freund, T.F., and Gulyás, A.I. (2001). Total number and distribution of inhibitory and excitatory synapses on hippocampal CA1 pyramidal cells. Neuroscience *102*, 527–540.

Mehta, M.R., Quirck, M.C., and Wilson, M.A. (2000). Experience-dependent asymmetric shape of hippocampal receptive fields. Neuron *25*, 707–715.

Miller, R. (1989). Cortico-hippocampal interpay: self-organizing phase-locked loops for indexing memories. Psychobiology *17*, 115–128.

Mitchell, S.J., and Ranck, J.B. (1980). Generation of theta rhythm in medial entorhinal cortex of freely moving rats. Brain Res. *189*, 49–66.

Mitzdorf, U. (1985). Current source-density method and application in cat cerebral cortex: investigation of evoked potentials and EEG phenomena. Physiol. Rev. *65*, 37–100.

Mizumori, S.J., Barnes, C.A., and McNaughton, B.L. (1990). Behavioral correlates of theta-on and theta-off cells recorded from hippocampal formation of mature young and aged rats. Exp. Brain Res. *80*, 365–373.

Monmaur, P., Thomson, M.A., and M'Harzi, M. (1986). Temporal changes in hippocampal theta activity following twenty minutes of forebrain ischemia in the chronic rat. Brain Res. *378*, 262–273.

Moroni, F., Corradetti, F., Moneti, G., and Pepeu, G. (1981). The release of endogenous GABA and glutamate from the cerebral cortex in the rat. Naunun-Schmiedeberg's Arch. Pharmacol. *316*, 235–239.

Moruzzi, G., and Magoun, H.W. (1949). Brainstem reticular formation and activation of the EEG. Electroencephal. Clin. Neurophysiol. *1*, 455–473.

O'Keefe, J., and Nadel, L. (1978). The hippocampus as a Cognitive Map (Clarendon, Oxford).

O'Keefe, J., and Recce, M.L. (1993). Phase relationship between hippocampal place units and the EEG theta rhythm. Hippocampus *3*, 317–330.

Otmakhova, N.A., and Lisman, J.E. (2000). Dopamine, serotonin, and noradrenaline strongly inhibit the direct perforant path-CA1 synaptic input, but have little effect on the Schaffer collateral input. Ann. N Y Acad. Sci. *911*, 462–464.

Paré, D., and Collins, D.R. (2000). Neuronal correlates of fear in the lateral amygdala: multiple extracellular recordings in conscious cats. J. Neurosci. *20*, 2701–2710.

Paulsen, O., and Sejnowski, T.J. (2000). Natural patterns of activity and long-term synaptic plasticity. Curr. Opin. Neurobiol. *10*, 172–179.

Pavlides, C., Greenstein, Y.J., Grudman, M., and Winson, J. (1988). Long-term potentiation in the dentate gyrus is induced preferentially on the positive phase of theta rhythm. Brain Res. *439*, 383–387.

Peet, M.J., Curry, K., Magnuson, D.S., and McLennan, H. (1987). The N-methyl-D-aspartate receptor and burst firing of CA1 hippocampal pyramidal neurons. Neuroscience *22*, 563–571.

Petsche, H., Stumpf, C., and Gogolák, G. (1962). The significance of the rabbit's septum as a relay station between midbrain and the hippocampus: I. The control of hippocampus arousal activity by the septum cells. Electroencephalogr. Clin. Neurophysiol. *14*, 202–211.

Pitler, T.A., and Alger, B.E. (1992). Cholinergic excitation of GABAergic interneurons in the rat hippocampal. J. Physiol. *450*, 127–142.

Pyapali, G.K., Sik, A., Penttonen, M., Buzsáki, G., and Turner, D.A. (1998). Dendritic properties of hippocampal CA1 pyramidal neurons in the rat: intracellular staining in vivo and in vitro. J. Comp. Neurol. *391*, 335–352.

Raghavachari, S., Kahana, M.J., Rizzuto, D.S., Caplan, J.B., Kirschen, M.P., Bourgeois, B., Madsen, J.R., and Lisman, J.E. (2001). Gating of human theta oscillations by a working memory task. J. Neurosci. *21*, 3175–3183.

Rose, G.M., and Dunwiddie, T.V. (1986). Induction of hippocampal long-term potentiation using physiologically patterned stimulation. Neurosci. Lett. *69*, 244–248.

Scanziani, M. (2000). GABA spillover activates postsynaptic GABA(B) receptors to control rhythmic hippocampal activity. Neuron *25*, 673–681.

Segal, M., Björklund, A., and Gage, F.H. (1985). Transplanted septal neurons make viable cholinergic synapses with a host. Brain Res. *336*, 302–307.

Semba, K., and Komisaruk, B.R. (1978). Phase of the theta wave in relation to different limb movements in awake rats. Electroencephalogr. Clin. Neurophysiol. *44*, 61–71.

Serafin, M., Williams, S., Khateb, A., Fort, P., and Muhlethaler, M. (1996). Rhythmic firing of medial septum non-cholinergic neurons. Neuroscience *75*, 671–675.

Sherrington, C.S. (1897). The central nervous system. In A Text Book of Physiology, part 3, M. Foster, ed. (Macmillan: London).

Sik, A., Ylinen, A., Penttonen, M., and Buzsáki, G. (1994). Inhibitory CA1–CA3-hilar region feedback in the hippocampus. Science *265*, 1722–1724.

Sik, A., Penttonen, M., Ylinen, A., Buzsáki, G. (1995). Hippocampal CA1 interneurons: an in vivo intracellular labeling study. J. Neurosci *15*, 6651–6665.

Sik, A., Penttonen, M., and Buzsáki, G. (1997). Interneurons in the hippocampal dentate gyrus: an in vivo itnracellular study. Eur. J. Neurosci. *9*, 573–588.

Skaggs, W.E., McNaughton, B.L., Wilson, M.A., and Barnes, C.A.

(1996). Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. Hippocampus *6*, 149–173.

Soltesz, I., and Deschénes, M. (1993). Low- and high-frequency membrane potential oscillations during theta activity in CA1 and CA3 pyramidal neurons of the rat hippocampus under ketamine-xylazine anesthesia. J. Neurophysiol. *70*, 97–116.

Spruston, N., Schiller, Y., Stuart, G., and Sakmann, B. (1995). Activity-dependent action potential invasion and calcium influx into CA1 dendrites. Science *268*, 297–300.

Steriade, M. (2000). Corticothalamic resonance, states of vigilance and mentation. Neuroscience *101*, 243–276.

Stewart, M., and Fox, S.E. (1990). Do septal neurons pace the hippocampal theta rhythm? Trends Neurosci. *13*, 163–168.

Strata, F. (1998). Intrinsic oscillations in CA3 hippocampal pyramids: physiological relevance theta rhythm generation. Hippocampus *8*, 666–679.

Tesche, C.D., and Karhu, J. (2000). Theta oscillations index human hippocampal activation during a working memory task. Proc. Natl. Acad. Sci. USA *97*, 919–924.

Tsubokawa, H., and Ross, W.N. (1996). IPSPs modulate spike backpropagation and associated [Ca2+]i changes in the dendrites of hippocampal CA1 pyramidal neurons. J. Neurophysiol. *76*, 2896–2906.

Tsubokawa, H., and Ross, W.N. (1997). Muscarinic modulation of spike backpropagation in the apical dendrites of hippocampal CA1 pyramidal neurons. J. Neurosci. *17*, 5782–5791.

Tóth, K., Borhegyi, Z., and Freund, T.F. (1993). Postsynaptic targets of GABAergic hippocampal neurons in the medial septum-diagonal band of broca complex. J. Neurosci. *13*, 3712–3724.

Tóth, K., Freund, T.F., and Miles, R. (1997). Disinhibition of rat hippocampal pyramidal cells by GABAergic afferents from the septum. J. Physiol. (Lond.) *500*, 463–474.

Traub, R.D., Miles, R., and Buzsáki, G. (1992). Computer simulation of carbachol-driven rhythmic population oscillations in the CA3 region of the in vitro rat hippocampus. J. Physiol. (Lond.) *451*, 653–672.

Tsodyks, M.V., Skaggs, W.E., Sejnowski, T.J., and McNaughton, B.L. (1996). Population dynamics and theta rhythm phase precession of hippocampal place cell firing: a spiking neuron model. Hippocampus *6*, 271–280.

Turner, D.A., Li, X.G., Pyapali, G.K., Ylinen, A., and Buzsáki, G. (1995). Morphometric and electrical properties of reconstructed hippocampal CA3 neurons recorded in vivo. J. Comp. Neurol. *356*, 580–594.

Van der Linden, S., Panzica, F., and De Curtis, M. (1999). Carbachol induces fast oscillations in the medial but not in the lateral entorhinal cortex of the isolated guinea pig brain. J. Neurophysiol. *82*, 2441–2450.

Vanderwolf, C.H. (1969). Hippocampal electrical activity and voluntary movement in the rat. Electroencephalogr. Clin. Neurophysiol. *26*, 407–418.

Vanderwolf, C.H. (1988). Cerebral activity and behavior: control by central cholinergic and serotonergic systems. Int. Rev. Neurobiol. *30*, 225–340.

Vanderwolf, C.H., and Leung, L.S. (1983). Hippocampal rhythmical slow activity: a brief history and effects entorhinal lesions and phencycidine. The Neurobiology of the Hippocampus, W. Seifert, ed. (London: Academic Press), pp. 275–302..

Vertes, R.P., and Kocsis, B. (1997). Brainstem-diencephalo-septohippocampal systems controlling the theta rhythm of the hippocampus. Neuroscience *81*, 893–926.

Vinogradova, O.S. (1995). Expression, control, and probable functional significance of the neuronal theta-rhythm. Prog. Neurobiol. *45*, 523–583.

Vizi, E.S., and Kiss, J.P. (1998). Neurochemistry and pharmacology of the major hippocampal transmitter systems: synaptic and nonsynaptic interactions. Hippocampus *8*, 566–607.

Wallenstein, G.V., and Hasselmo, M.E. (1997). GABAergic modulation of hippocampal population activity: sequence learning, place field development, and the phase precession effect. J. Neurophysiol. *78*, 393–408.

Wang, X.-J. (2002). Pacemaker neurons for the theta rhythm and their synchronization in the septo-hippocampal reciprocal loop. J. Neurophysiol. *87*, 889–900.

Westenbroek, R.E., Ahlijanian, M.K., and Catterall, W.A. (1990). Clustering of L-type Ca2+ channels at the base of major dendrites in pyramidal neurons. Nature *347*, 281–284.

Whishaw, I.Q. (1976). Neuromuscular blockade: the effects on two hippocampal RSA (theta) systems and neocortical desynchronization. Brain Res. Bull. *1*, 573–581.

Whishaw, I.Q., Bland, B.H., and Bayer, S.A. (1978). Postnatal hippocampal granule cell agenesis in the rat: effects on two types of rhythmical slow activity (RSA) in two hippocampal generators. Brain Res. *146*, 249–268.

Williams, J.H., and Kauer, J.A. (1997). Properties of carbachol-induced oscillatory activity in rat hippocampus. J. Neurophysiol. *78*, 2631–2640.

Wilson, M.A., and McNaughton, B.L. (1993). Dynamics of the hippocampal ensemble code for space. Science *261*, 1055–1058.

Wilson, R.I., and Nicoll, R.A. (2001). Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature *410*, 588–592.

Winson, J. (1974). Patterns of hippocampal theta rhythm in freely moving rat. Electroencephalogr. Clin. Neurophysiol. *36*, 291–301.

Ylinen, A., Soltesz, I., Bragin, A., Penttonen, M., Sik, A., and Buzsáki, G. (1995). Intracellular correlates of hippocampal theta rhythm in identified pyramidal cells, granule cells and basket cells. Hippocampus *5*, 78–90.