Theta-frequency synchronization of hippocampal CA1 populations by hyperpolarization-activated currents

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ABSTRACT

Theta (3-8 Hz) is a major hippocampal electrophysiological activity with distinct firing profiles for hippocampal neuron populations. In our computational study, we used a three-population network to investigate how timing of distinct neuron populations can emerge. We have shown that the intrahippocampal circuitry is able to generate coherent theta-frequency oscillation. Furthermore, we found that hyperpolarization-activated current in pyramidal cells, but not in O-LM neurons, plays an important role in the timing, and synchronization of pyramidal cells. The model was shown to exhibit the same timing relationship found in vivo, supporting the idea that the hippocampus itself is a significant contributor to the coherent theta oscillation.

Introduction

Generation of hippocampal theta activity was addressed by numerous computational and experimental studies. Despite the extensive literature on the pharmacological profile ([1]) and the detailed physiology of participating neuron populations ([2]), no settled view is available on its generation. The precise firing relationship of hippocampal neuron populations *in vivo* ([3, 4]) necessitates a mechanism that enables neuron populations with highly variable physiological properties to fire synchronously.

Recently, it has been shown *in vitro* that theta can emerge in a CA1 slice by the activation of metabotropic glutamate receptors and with a timing of neuron populations similar to the one observed *in vivo*. A characteristic feature of this *in vitro* model was that it was sensitive to the blockade of conductance of the hyperpolarization-activated non-specific cation current (I_h). Although it is known that I_h is present in multiple cell populations, including pyramidal ([5]) and O-LM cells ([6]), the identity of those effectively contributing the generation of theta oscillation was not determined.

In the present computational study we investigated the conditions necessary for the emergence of theta oscillation in the hippocampal CA1 circuitry. Contribution of I_h to the generation of hippocampal theta was first explored and we aimed at providing data how the presented scenario is relevant in *in vivo* conditions. Also, we briefly addressed the question what roles glutamate receptors play in this scenario of theta generation.

Methods

The hippocampal CA1 model featured three neuron populations including pyramidal neurons, oriens–lacunosum moleculare interneurons (O-LM cells) and basket interneurons. The multicompartmental pyramidal cell model was based on the model of Warman et al. (1994), extended with additional hyperpolarization-activated current (I_h). Basket neurons were single compartmental realizations ([8, 9]), for O-LM interneurons the model of Wang (2002) was adopted.

Pattern of synaptic connectivity was determined according to available anatomical data. Basket cells projected principally to the perisomatic region of pyramidal neurons. Because of the sparse recurrent collaterals in the CA1 region a smaller number of pyramidal cells were used ([11]).

Basket neurons innervated other basket neurons,divergence was 60. O-LM cells projected both to pyramidal cells ([12, 13]) and basket neurons ([14]) establishing contacts through $GABA_A$receptor mediated synapses. The main excitatory input to the O-LM neurons derives from CA1 recurrent connections ([15, 16]). In our network model, pyramidal cells projected to O-LM cells using glutamatergic synapses. Synaptic transmission was mediated by either AMPA ([17, 18]) or NMDA receptors ([19]) or both. Pyramidal cells were shown to innervate basket neurons as well ([20]), however, NMDA receptor mediated synaptic currents were not included as it has been shown that in the CA1 region of the hippocampus NMDA receptors dominate in O-LM cells over parvalbumin positive cells ([19]). Population sizes in the simulations shown (if not stated otherwise) were 100, 60, and 16 for basket cells, O-LM cells, and pyramidal cells, respectively.

Extracellular field potential was calculated using data obtained from pyramidal cells by calculating the total transmembrane current and divided by the distance of the compartment the current derived from. The overwhelmingly larger number of pyramidal cells in the real neural tissue legitimated the method of using only pyramidal cell activity for this calculation.

Phase distribution histograms. Firing histograms as a function of phase of a reference signal were prepared. Reference signal was acquired from the hippocampal CA1 field potential by filtering it with a Gaussian filter. Phase (ϕ) of an action potential in degrees relative to the reference signal is calculated by the $\phi = 360^\circ (t - T_1) / (T_2 - T_1)$ equation, where t is the time of action potential occurrence, T_1 and T_2 are times of local maxima of the reference signal preceding and succeeding t, respectively. Mean of phase distribution histograms was calculated by calculating circular mean of the histogram, in the form $\mu_p = P/2\pi \left(\arg \left(\sum_{k=1}^{N} \exp \left(i2\pi\alpha (k) / P \right) \right) \right)_{2\pi}$. Angular deviation was calculated as $\sigma_p = P/2\pi \sqrt{\sum_{k=1}^{N} \left(\arg \left(\exp \left(i2\pi \left| \mu_p - \alpha (k) \right| / P \right) \right) \right)^2}$

Results

Due space limitations, pairwise population interactions are not discussed. However, an aspect of basket-to-pyramidal cell interaction is detailed below.

Rebound action potentials of pyramidal cells proved to be crucial for the synchronization of pyramidal cell activity. Therefore, we investigated the mechanism underlying this phenomenon. The role of I_h current in the induction of rebound action potentials was investigated (Fig. 1). Rebound action-potential generation with decreased I_h conductance required more hyperpolarized membrane. Without I_h current no rebound action-potential could be generated in physiological circumstances. Hyperpolarization evoked action potential generation required the least injected current when the apical dendritic compartment approximately 200 μm far from the soma was clamped. Simulation results revealed an optimal length of clamping time window, at which minimal hyperpolarizing current evoked an action potential (Fig. 1D).

The hippocampal loop formed by pyramidal cells and two classes of interneurons was able to generate theta-frequency oscillation as reflected by the EEG calculated from the activity of pyramidal neurons (Fig. 2B, see Methods) and firing histograms (Fig. 2A). To faithfully follow the protocol applied *in vitro*, synaptic transmission through AMPA synapses was suppressed. In the hippocampal CA1 loop, activity of pyramidal cells affects the frequency of disinhibition via the excitation exerted by their recurrent collaterals innervating O-LM and basket cells, thus this feedback is capable of entraining a larger frequency collective oscillation. We systematically changed the depolarizing current delivered to the pyramidal cells. Simulations revealed a monotonous increase in EEG theta frequency over a wide range of tonic depolarizing current levels (Fig. 2E).

As depolarization level of pyramidal cells has an effect on theta frequency, we investigated whether the oscillation is robust against variations in this factor. Depolarizing current was set inhomogeneously, that is, while delivering constant currents to the pyramidal cells the level was determined in a random manner. Simulations confirmed that this kind of irregularity can not disrupt the synchro-

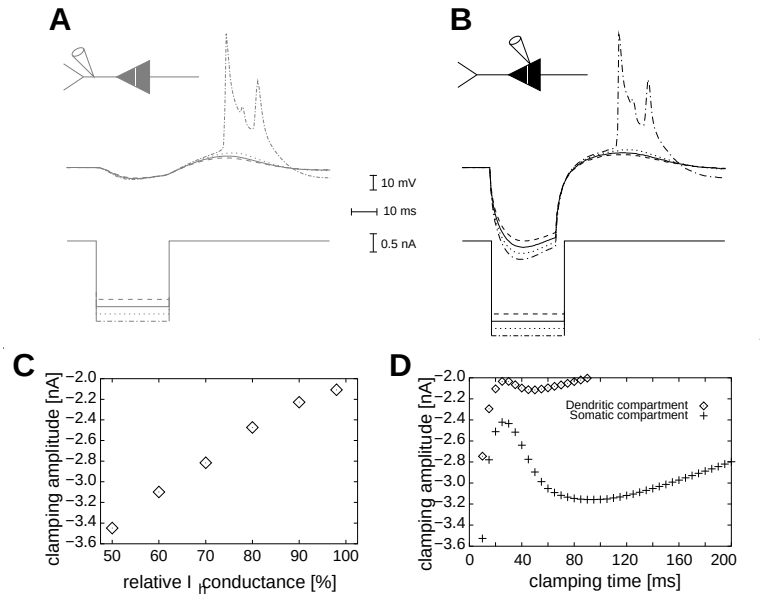

Figure 1: While pyramidal cell model was current clamped at different membrane regions by hyperpolarizing current steps, conditions of rebound action potential generation were studied. A and B, typical membrane potential traces of the soma are shown as a result of clamping the soma and part of the dendritic branch of the pyramidal cell, respectively. C, Maximal conductance of I_h current was selectively and systematically varied in the $50 - 100$ % interval while minimal current necessary to evoke action potential was registered. D, Comparison between clamping the somatic and a dendritic region 200 μm apart from the soma.

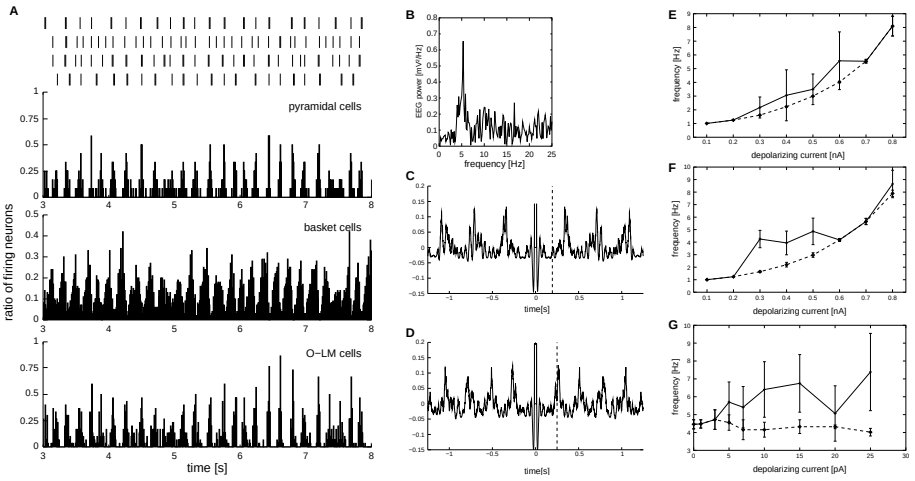

Figure 2: Characterization of the theta frequency population oscillation using the three-population network model. A, Firing histograms of neuron populations. *Ticks:* sample spike trains of four randomly chosen pyramidal cells. B, Power spectrum of extracellular field potential. C, D, auto-correlograms of two randomly chosen pyramidal cells at 0.5 and 0.6 nA inducing current, respectively. *Dashed line* period of theta oscillation, as reflected by the EEG power. E, F, Mean frequency of the theta activity as a function of depolarization of pyramidal cells. Level of depolarization was either set homogeneously at each pyramidal cell (E), or was picked from a Gaussian distribution with a mean indicated on the y-axis and SD of 5% (F). *Solid line:* Mean frequency calculated from the power spectrum of low-pass filtered ($1 - 15$ Hz) EEG, *dashed line:* Mean peak frequency of power spectrum calculated from membrane potential traces of individual pyramidal cells, averaged over different trials ($n = 8$). G, Mean EEG frequency as a function of O-LM cell depolarization.

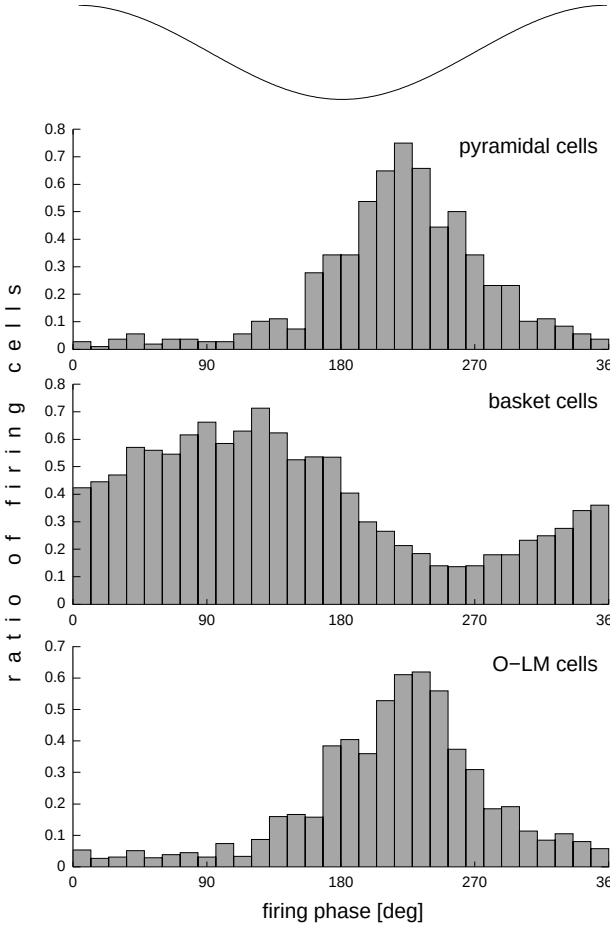

Figure 3: Action potential timing of different cell populations relative to extracellular theta oscillation. Phase distribution histograms (PDHs) of neuron populations. *Upper trace:* Demonstration of a field theta oscillation epoch. Comparing results obtained for different depolarization levels, i.e. different frequencies, a similar phase relationship could be established (Fig. 3B).

nization of cell populations (Fig. 2F). Obviously, changes in resting membrane potentials of pyramidal cells did not disrupt theta frequency oscillation either (data not shown). Similarly, we tested whether altered firing properties of O-LM neurons can affect the frequency of population oscillation (Fig. 2G).

Calculating firing phase histograms revealed a nearly equal mean firing phase of the pyramidal cell population and O-LM cell population with a $2.2 \pm 1.9°$ lag of pyramidal cells. Basket cells preceded pyramidal cells by $127.2 \pm 3.5°$ (Fig. 3A).

We investigated network performance while different types of ionotropic glutamate receptors were modulated separately. Theta could emerge in our network when the only excitatory synaptic transmission was realized by NMDA synapses (Fig. 2). Including AMPA receptor mediated synaptic currents did not alter the power of theta oscillation significantly (Fig. 4). However, a significant in-

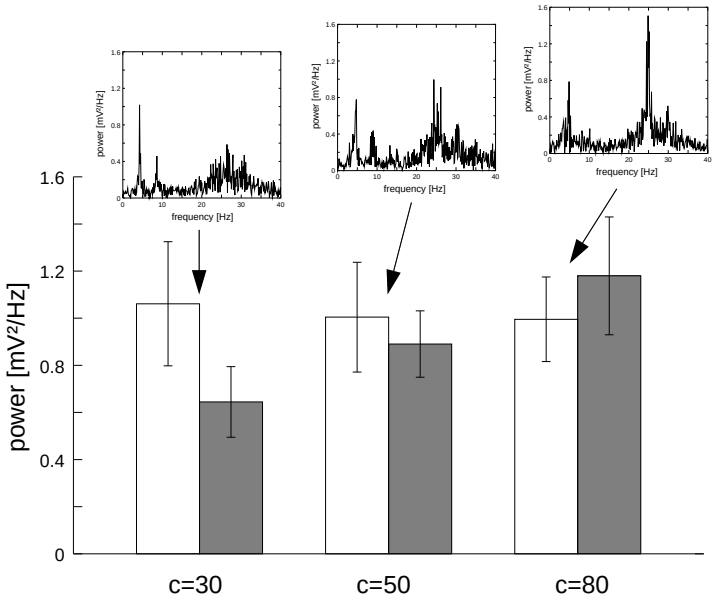

Figure 4: Effect of increasing divergence (c) of pyramidal cells on basket interneurons. *White bars* show mean theta power, while *grey bars* show mean gamma power. *Insets:* sample power spectra at different convergence levels. With increasing convergence levels gamma-band activity is enhanced.

crease was observed in the power at the gamma frequency-band ($20 - 80$ Hz, Fig. 4 insets), corresponding to the more effective gamma-gating of fast-spiking basket cells. This observation was further confirmed by the fact that increasing the convergence of pyramidal cells on basket neurons resulted in higher gamma activity (Fig. 4). The effect was even more expressed when exclusively AMPA synapses were present on basket neurons (data not shown).

Next, we investigated the case when depolarization of pyramidal cells was dispersed and conductance of I_h at network components was changed. In the model framework I_h was present both in pyramidal cells and O-LM interneurons. First, I_h conductance was set to 0 pS at both populations. Eliminating I_h caused the attenuation of theta peak in the power spectrum of EEG (Fig. 5B,C). Contribution of I_h was also investigated by reducing I_h conductance selectively at pyramidal cells and O-LM interneurons. Simulations have shown that reducing I_h at O-LM interneurons does not result in reduced theta amplitude (data not shown). However, a reduction of 55% was observable at simulations performed with blocked I_h at pyramidal cells.

Conclusions

The current study aimed at providing evidence that the circuitry of hippocampal region CA1 is endowed with the ability to generate theta-frequency population oscillations with timing of neuron populations corresponding to those measured in experiments. We demonstrated that the presence of hyperpolarization-

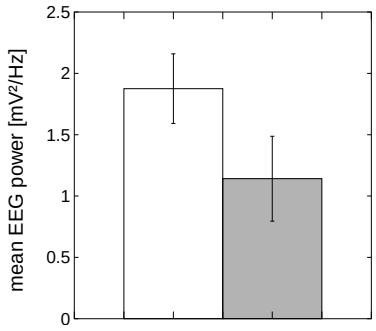

Figure 5: Contribution of I_h to theta oscillation. Control simulations were conducted with I_h current blocked both on pyramidal cells and O-LM neurons. Depolarization of pyramidal cells was different for each cell, its level was picked from a Gaussian distribution. Simulations testing contribution of I_h were performed with blocked I_h conductance at both cells types. Mean amplitude of theta power is shown. (*Grey bar*) blocked I_h in the whole network as compared to the power in the network with intact I_h (*white bar*).

activated non-specific cation current (I_h) greatly enhances the synchronization properties of the CA1 network. Indeed, while without I_h synchronization was possible under circumstances where frequency characteristics were the same for all pyramidal neurons, with I_h the network was robust against variations. We propose that timing and thus synchronization of pyramidal cells is brought about by rebound spikes. Rebound spikes are facilitated by the opening of hyperpolarization-activated non-specific cation channels. Emerging theta activity is robust against variations in network structure, as reflected by the random connection patterns, and variations in frequencies of individual pyramidal cells, as reflected by depolarizing currents set in a random fashion. We showed that the widely acknowledged role of NMDA conductances might rely on mechanisms intrinsic to the hippocampus, and are effective in synchronizing the activity of hippocampal neurons. Finally, We argue that phase relationships characteristic to hippocampal neuron populations during theta rely on the intrahippocampal circuitry.

References

[1] R. P. Vértes, B. Kocsis, Brainstem-diencephalo-septohippocampal systems controlling the theta rhythm of the hippocampus, Neuroscience 81 (1997) 893–926.

[2] G. Buzsáki, Theta oscillations in the hippocampus, Neuron 33 (2002) 325–340.

[3] J. Csicsvári, H. Hirase, A. Czurkó, A. Mamiya, G. Buzsáki, Oscillatory coupling of hippocampal pyramidal cells and interneurons in the behaving rat, J. Neurosci 19 (1) (1999) 274–87.

[4] T. Klausberger, P. J. Magill, L. F. Márton, J. D. B. Roberts, P. M. Cobden, G. Buzsáki, P. Somogyi, Brain-state- and cell-type-specific firing of hippocampal interneurons in vivo, Nature 421 (2003) 844–8.

[5] J. Magee, Dendritic hyperpolarization-activated currents modify the integrative properties of hippocampal CA1 pyramidal neurons, J. Neurosci. 18 (19) (1998) 7613–7624.

[6] G. Maccaferri, C. J. McBain, The hyperpolarization-activated current (ih) and its contribution to pacemaker activity in rat ca1 hippocampal stratum oriens-alveus interneurones, J. Physiol. 497 (1996) 119–30.

[7] E. N. Warman, D. M. Durand, G. L. Yuen, Reconstruction of hippocampal CA1 pyramidal cell electrophysiology by computer simulation, J. Neurophysiol. 6 (1994) 2033–45.

[8] X. J. Wang, G. Buzsáki, Gamma oscillation by synaptic inhibitionin a hippocampal interneuronl network model, J. Neurosci. 16 (1996) 6402–6413.

[9] G. Orbán, T. Kiss, M. Lengyel, P. Érdi, Hippocampal rhythm generation: Gamma-related theta-frequency resonance in CA3 interneurons, Biol. Cybern. 84 (2001) 123–132.

[10] X. J. Wang, Pacemaker neurons for the theta rhythm and their synchronization in the septohippocampal reciprocal loop, J. Neurophysiol. 87 (2) (2002) 889–900.

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

[12] A. I. Gulyás, R. Miles, N. Hájos, T. F. Freund, Precision and variability in postsynaptic target selection of inhibitory cells in the hippocampal ca3 region, Eur. J. Neurosci. 5 (1993) 1729–51.

[13] C. J. McBain, T. J. DiChiara, J. A. Kauer, Activation of metabotropic glutamate receptors differentially affects two classes of hippocampal interneurons and potentiates excitatory synaptic transmission, J. Neurosci. 14 (1994) 4433–45.

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

[15] J. M. Blasco-Ibanez, T. F. Freund, Synaptic input of horizontal interneurons in stratum oriens of the hippocampal ca1 subfield: structural basis of feed-back activation, Eur. J. Neurosci. 7 (1995) 2170–80.

[16] J. C. Lacaille, A. L. Mueller, D. D. Kunkel, P. A. Schwartzkroin, Local circuit interactions between oriens/alveus interneurons and ca1 pyramidal cells in hippocampal slices: electrophysiology and morphology, J. Neurosci. 7 (1987) 1979–93.

[17] A. Baude, Z. Nusser, E. Molnár, R. A. McIlhinney, P. Somogyi, High-resolution immunogold localization of ampa type glutamate receptor subunits at synaptic and non-synaptic sites in rat hippocampus, Neuroscience 69 (1995) 1031–55.

[18] Z. Nusser, R. Lujan, G. Laube, J. D. Roberts, E. Molnár, P. Somogyi, Cell type and pathway dependence of synaptic ampa receptor number and variability in the hippocampus, Neuron 21 (1998) 545–59.

[19] G. Nyíri, F. A. Stephenson, T. F. Freund, P. Somogyi, Large variability insynaptic N-methyl-D-aspartate receptor density on interenurons and a comparison with pyramidal-cell spines in the rat hippocampus, Neuroscience 119 (2003) 347–363.

[20] A. I. Gulyas, R. Miles, A. Sik, K. Toth, N. Tamamaki, T. F. Freund, Hippocampal pyramidal cells excite inhibitory neurons through a single release site, Nature 366 (1993) 683–7.