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A computational study on how theta modulated inhibition can account for the long temporal windows in the entorhinal–hippocampal loop

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ABSTRACT

A recent experimental study (Mizuseki, Sirota, Pastalkova, & Buzsaki, 2009) has shown that the temporal delays between population activities in successive entorhinal and hippocampal anatomical stages are longer (about 70–80 ms) than expected from axon conduction velocities and passive synaptic integration of feed-forward excitatory inputs. We investigate via computer simulations the mechanisms that give rise to such long temporal delays in the hippocampus structures. A model of the dentate gyrus (DG), CA3 and CA1 microcircuits is presented that uses biophysical representations of the major cell types including granule cells, CA3 and CA1 pyramidal cells (PCs) and six types of interneurons: basket cells (BCs), axo-axonic cells (AACs), bistratified cells (BSCs), oriens lacunosum-moleculare cells (OLMs), mossy cells (MCs) and hilar perforant path associated cells (HC). Inputs to the network came from the entorhinal cortex (EC) (layers 2 and 3) and the medial septum (MS). The model simulates accurately the timing of firing of different hippocampal cells with respect to the theta rhythm. The model shows that the experimentally reported long temporal delays in the DG, CA3 and CA1 hippocampal regions are due to theta modulated somatic and axonic inhibition. The model further predicts that the phase at which the CA1 PCs fire with respect to the theta rhythm is determined primarily by their increased dendritic excitability caused by the decrease of the axial resistance and the A-type K^+ conductance along their dendritic trunk. The model predicted latencies by which the DG, CA3 and CA1 principal cells fire are inline with the experimental evidence. Finally, the model proposes functional roles for the different inhibitory interneurons in the retrieval of the memory pattern by the DG, CA3 and CA1 networks. The model makes a number of predictions, which can be tested experimentally, thus leading to a better understanding of the biophysical computations in the hippocampus.

1. Introduction

The EC and hippocampus formation (HF) have been studied extensively yielding a wealth of data on cell types and their passive and active properties, network architecture and synaptic plasticity (Andersen, Morris, Amaral, Bliss, & O'Keefe, 2007; Cutsuridis, Graham, Cobb, & Vida, 2010). HF contains principal excitatory neurons (GCs in DG and PCs in regions CA3 and CA1) and a large variety of excitatory and inhibitory interneurons (Freund & Buzsaki, 1996; Somogyi & Klausberger, 2005). The cells in different HF regions compute information differently. DG has been implicated in pattern separation (Marr, 1971; McNaughton & Morris, 1987; Wilson & McNaughton, 1993; Hasselmo & Wyble, 1997;), CA3 in pattern completion (Marr, 1971; McNaughton & Morris, 1987) and CA1 in novelty detection (Vinogradova, 2001) and mismatch of expectations (Hasselmo & Schnell, 1994). Local computation within each HF region takes time creating temporal windows of excitability, which are evident by local field potentials (LFPs) (Buzsaki, 2002).

Theta rhythm (4–10 Hz) is one such LFP (Alonso & Garcia-Austt, 1987; Grastyan, Lissak, Madarasz, & Donhoffer, 1959; Vanderwolf, 1969) and it has been shown to play an instrumental role in the coordination of neuronal firing in the entorhinal–hippocampal network (Buzsaki, 2002). Theta oscillations have also been implicated in the encoding and retrieval of episodic and spatial memories (Cutsuridis, Cobb, & Graham, 2008, 2010; Cutsuridis & Hasselmo, 2012; Cutsuridis & Wenneckers, 2009; Hasselmo, Bodelon, & Wyble, 2002; Jensen & Lisman, 2005; Kunec, Hasselmo, & Kopell, 2005) and disruption of them results in behavioral deficits (Winson, 1978). Theta rhythm in HF is paced by MS and diagonal band of Broca in the basal forebrain (Stewart & Fox, 1990; Winson, 1978), although several theta generators and theta dipoles seem to work independently in the hippocampus (Buzsaki, 2002;

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Montgomery, Betancur, & Buzsaki, 2009). One such theta oscillator is recorded in the stratum lacunosum moleculare (SLM) in CA1, while two other are recorded in stratum moleculare (SM) in DG and stratum pyramidale (SP) in CA1 (Brankack, Stewart, & Fox, 1993). The SLM theta oscillator oscillates at opposite phase with the SM and SP oscillators, which oscillate in phase with each other (Brankack et al., 1993). Current source density studies (Brankack et al., 1993) have shown that theta in other layers in CA1 show intermediate to SLM and SM phase relations. Theta oscillations are also recorded in EC and show a phase inversion between layers I and II–V (Alonso & Garcıa-Austt, 1987; Mizuseki, Sirota, Pastalkova, & Buzsaki, 2009). EC layers II and III, which project to HF (DG, CA3 and CA1), oscillate in phase (Mizuseki et al., 2009), and this phase is similar to the one in CA1 SP (Mizuseki et al., 2009).

Excitation and inhibition in HF come in different flavors (Freund & Buzsaki, 1996; Klausberger & Somogyi, 2008). Inhibition in particular sculpts the activities of excitatory cells (GCs in DG and PCs in CA3 and CA1), thus allowing them to fire at particular temporal windows and phases with respect to external network oscillations (Klausberger & Somogyi, 2008; Mizuseki et al., 2009). At least 25 different types of inhibitory interneurons have been identified in regions DG, CA3 and CA1 of the hippocampus (Fuentealba et al., 2008; Jinno et al., 2007; Klausberger et al., 2005; Somogyi, Katona, Klausberger, Lasztoczi, & Viney, 2014; Vida, 2010). These include AACs, the perisomatic BCs and the dendritic BSCs, ivy (IVY), neurogliaform (NGL), OLMs and HC cells (Capogna, 2011; Freund & Buzsaki, 1996; Fuentealba et al., 2008a, 2008b; Fuentealba et al., 2010). AACs innervate exclusively the initial axonal segment of the DG GCs and the CA3 and CA1 PCs, whereas BCs innervate their cell bodies and proximal dendrites (Somogyi & Klausberger, 2005; Vida, 2010). CA1's BSCs and IVYs innervate the CA1 PC basal and oblique dendrites, whereas OLM and NGL cells target the apical dendritic tuft of CA3 and CA1 PCs aligned with the EC input (Capogna, 2011; Somogyi et al., 2014). The DG HC cells target the apical dendrites of the DG GCs (Vida, 2010).

DG, CA3 and CA1 cells discharge at different phases of theta oscillations (Capogna, 2011; Fuentealba et al., 2008a, 2008b, 2010; Klausberger & Somogyi, 2008; Mizuseki et al., 2009; Somogyi et al., 2014). CA1 OLMs, BSCs, IVYs and PCs fire at the trough of theta recorded in the CA1 SP, whereas CA1 AACs, BCs and NGLs fire at the peak of theta recorded in the CA1 SP (Fuentealba et al., 2008a, 2008b, 2010; Klausberger & Somogyi, 2008). CA3 AACs fire rhythmically around the peak of the theta oscillations recorded locally in CA3 (Viney et al., 2013), whereas CA3 BCs and PCs fire around the trough of the local CA3 theta with the PCs firing leading the BCs firing by few degrees (Tukker et al., 2013). CA3 OLMs, which are recurrently excited by the CA3 PCs should fire at the trough of CA3 theta right after the CA3 PCs. In addition to hippocampal cells, MS cell activities are theta modulated (Borhegyi, Varga, Szilagyi, Fabo, & Freund, 2004; Dragoi, Carpi, Recce, Csicsvari, & Buzsaki, 1999; Stumpf, Petsche, & Gogolak, 1962). GABAergic MS neurons form two distinct populations exhibiting highly regular bursting activity that is coupled to either the trough or the peak of hippocampal theta waves (Borhegyi et al., 2004).

A recent seminal paper by Mizuseki et al. (2009) reported that the temporal delays between population activities in successive stages of the EC–hippocampal loop are considerably longer (about a half theta cycle) than previously reported during theta-associated behaviors and these delays could not be accounted for by axon conduction delays, synaptic delays and/or neuronal integration of feedforward excitatory inputs. They suggested that one of the potential physiological mechanisms for such long temporal delays is inhibition (see p. 277 in Mizuseki et al., 2009).

Building on their suggestion, we explored via computational modelling the role of theta modulated intra- and extra-hippocampal inhibition in the generation of longer than a theta half-cycle delays of neuronal excitability in successive hippocampal stages (DG, CA3 and CA1). We constructed a microcircuit model of the hippocampal formation (regions DG, CA3 and CA1) that used biophysical representations of the major cell types including GCs, CA3 and CA1 PCs and six types of interneurons: BCs, AACs, BSCs, OLMs, MCs and HC cells. Theta modulated inputs at alternate phases and strengths to the network came from the entorhinal cortex (layers 2 and 3) and the MS. The model simulated the timing of firing of different hippocampal cells with respect to the theta rhythm (Klausberger & Somogyi, 2008; Mizuseki et al., 2009; Somogyi et al., 2014; Tukker et al., 2013; Viney et al., 2013) and showed that the experimentally reported long temporal delays in the successive hippocampal regions (Mizuseki et al., 2009) are indeed due to theta modulated somatic and axonic inhibition. Our model also predicted that the phase at which the CA1 PCs fire with respect to the EC-L3 theta LFP (see Fig. 3) is determined by their increased dendritic excitability caused by the decrease of the axial resistance and the A-type K^+ conductance along their dendritic trunk (Golding, Mickus, Katz, Kath, & Spruston, 2005; Losonczy, Makara, & Magee, 2008). The model proposed functional roles for the different inhibitory interneurons in the retrieval of the memory pattern by the DG, CA3 and CA1 network. Finally, the model led to a number of experimentally testable predictions that may provide a better understanding of the biophysical computations in the hippocampus.

2. Materials and methods

Fig. 1 in the main text illustrates the simulated microcircuit model of the DG-CA3-CA1 network. The model consists of 100 DG GCs, 2 DG MCs, 2 DG BCs, 1 HC, 100 CA3 PCs, 2 CA3 BCs, 1 CA3 AAC, 1 CA3 OLM cell, 100 CA1 PCs, 1 CA1 AAC, 2 CA1 BCs, and 1 CA1 BSC. All simulations were performed using NEURON (Hines & Carnevale, 1997) running on a PC under Linux.

Simplified morphologies including the soma, apical and basal dendrites and a portion of the axon, were used for each cell type. The biophysical properties of each cell were adapted from cell types reported in the literature, which were extensively validated against experimental data in (Aradi & Holmes, 1999; Migliore, Cook, Jaffe, Turner, & Johnston, 1995; Poirazi, Brannon, & Mel, 2003a, 2003b; Santhakumar, Aradi, & Soltesz, 2005; Saraga, Wu, Zhang, & Skinner, 2003). The complete mathematical formalism of the model is described in the Supporting Online Material (SOM). Schematic representations of the model cells are depicted in Supplementary Figs. S1–S3. The dimensions of the somatic, axonic, and dendritic compartments of the model cells are presented in Supplementary Tables S1–S3. The parameters of all passive and active ionic conductances used in the model are listed in Supplementary Tables S4–S9. The synaptic waveform parameters are given in Supplementary Tables S10 and S11 and synaptic conductances are listed in Supplementary Tables S12–S14. Experimental support of the choices of the various parameters can be found in SOM.

2.1. DG granule cells

Each DG granule cell (Aradi & Holmes, 1999; Santhakumar et al., 2005) had 9 compartments (see Supplementary Fig. S1), each containing calcium pump and buffering mechanisms, slow and fast delayed rectifier K^+ currents, a sodium current, an A-type K^+ current, L-, N- and T-type Ca^{2+} currents, a large conductance calcium