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Inhibition-Induced Theta Resonance in Cortical Circuits

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SUMMARY

Both circuit and single-cell properties contribute to network rhythms. In vitro, pyramidal cells exhibit theta-band membrane potential (subthreshold) resonance, but whether and how subthreshold resonance translates into spiking resonance in freely behaving animals is unknown. Here, we used optogenetic activation to trigger spiking in pyramidal cells or parvalbumin immunoreactive interneurons (PV) in the hippocampus and neocortex of freely behaving rodents. Individual directly activated pyramidal cells exhibited narrow-band spiking centered on a wide range of frequencies. In contrast, PV photoactivation indirectly induced theta-band-limited, excess post-inhibitory spiking in pyramidal cells (resonance). PV-inhibited pyramidal cells and interneurons spiked at PV-inhibition troughs, similar to CA1 cells during spontaneous theta oscillations. Pharmacological blockade of hyperpolarization-activated (I_h) currents abolished theta resonance. Inhibition-induced theta-band spiking was replicated in a pyramidal cell-interneuron model that included I_h. Thus, PV interneurons mediate pyramidal cell spiking resonance in intact cortical networks, favoring transmission at theta frequency.

INTRODUCTION

Theta (4–11 Hz) oscillations provide a basis for temporal coding of spatial information and episodic memory in the hippocampus (O'Keefe and Recce, 1993; Buzsáki and Moser, 2013). The theta rhythm is generated by a consortium of mechanisms, including a septal pacemaker, circuit interactions, and intrinsic properties of single neurons (Buzsáki, 2002). A potentially important mechanism contributing to theta generation is the resonant properties of neurons (Leung and Yu, 1998; Dickson et al., 2000; Pike et al., 2000; Haas and White, 2002; Hu et al., 2002; Erchova et al., 2004; Lengyel et al., 2005; Giocomo et al., 2007; Gastrein et al., 2011). In general, resonance refers to an amplifying mechanism in a limited frequency band (Hutcheon and Yarom, 2000). In vitro, intracellular sinusoidal current injection into hippocampal pyramidal neurons yields subthreshold membrane potential oscillations with a maximum amplitude in the theta band (Leung and Yu, 1998; Pike et al., 2000; Hu et al., 2002; Zemankovics et al., 2010). Subthreshold theta-band resonance is largely mediated by the hyperpolarization-activated cyclic nucleotide-sensitive (HCN) channels, which generate a nonselective cation current, I_h (Gasparini and DiFrancesco, 1997; Robinson and Siegelbaum, 2003). HCN1 channels are especially abundant in the distal apical dendrites of CA1 and neocortical layer 5 pyramidal cells (Magee 1998; Stuart and Spruston, 1998; Santoro et al., 2000; Lörincz et al., 2002; Ulrich, 2002). The inductive effects of I_h create a negative feedback that opposes the voltage changes and thus creates resonance (Narayanan and Johnston, 2008). Because HCN1 channels are active at a hyperpolarized membrane potential, theta resonance in circuits is expected to depend on interaction between inhibitory interneurons and pyramidal cells. Indeed, theta-frequency burst discharge of hippocampal basket cells can effectively coordinate spike timing of target pyramidal neurons and induce rebound spikes after release from hyperpolarization in vitro (Cobb et al., 1995). Yet, it is not clear if and how subthreshold resonance is translated to the suprathreshold (spiking) regime (Magee, 1998; Pike et al., 2000; Ulrich, 2002; Richardson et al., 2003) in behaving animals.

Subsets of neurons in the neocortex can also phase-lock to hippocampal theta oscillations (Siapas et al., 2005; Sirota et al., 2008), possibly entrained by interneurons, but it is unknown whether resonance-related mechanism are involved in this process. More generally, it remains to be demonstrated whether neuronal spiking and interneuronal information transfer are sensitive to input at any specific frequency range. To determine the importance of input frequency for spiking activity in the intact hippocampus and neocortex, we examined spiking responses of pyramidal cells and interneurons to optogenetically induced membrane potential oscillations at various frequencies in freely behaving animals. Light activation was confined to a small group of nearby neurons (Stark et al., 2012) so that the cellular-synaptic mechanisms could be investigated without altering the network state or the oscillatory frequency/phase of native rhythms.

RESULTS

Pyramidal Cells Spike Preferentially in the Theta Band during Light-Induced PV Cell Activation

For cell type-specific control of neuronal spiking, mice expressing ChR2 (Boyden et al., 2005) either in pyramidal neurons

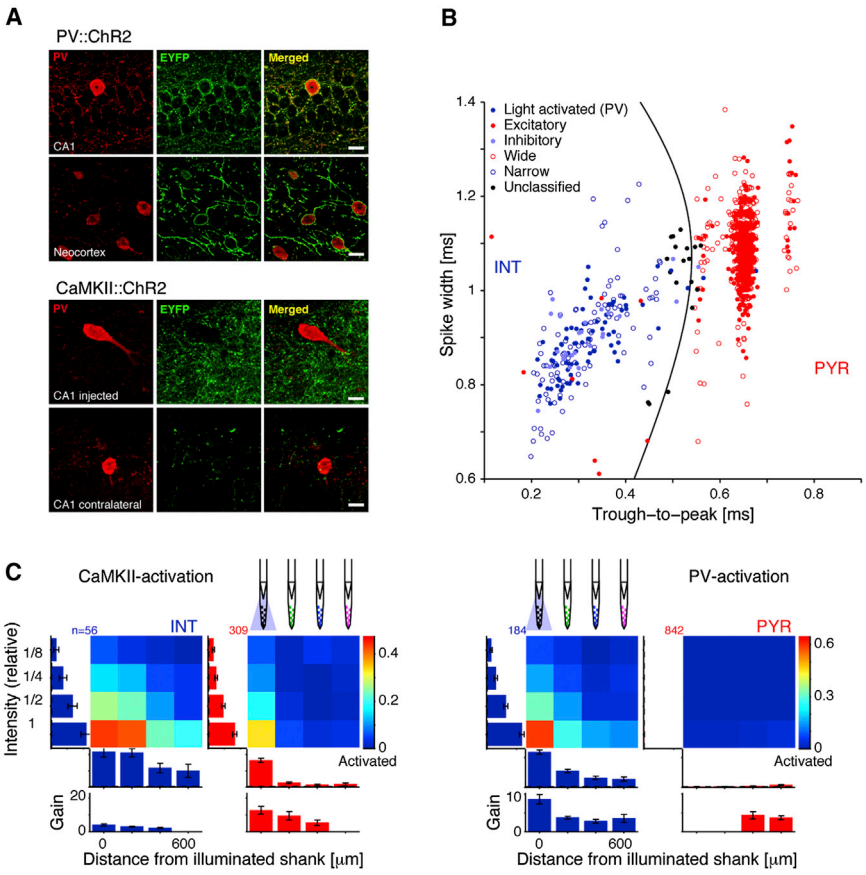

Figure 1. Local Activation of Specific Cell Types in Freely Moving Mice

(A) Immunostaining for PV colocalizes with EYFP, the reporter gene for ChR2 expression, in PV-cre::Ai32 mice but not in animals injected unilaterally with rAAV5/CamKIIa-hChR2(h134R)-EYFP viruses. In five PV-cre::Ai32 animals, all 84 EYFP+ cells were PV+ (100%) and 84 of 93 PV+ cells were EYFP+ (90%). Calibration, 15 μm.

(B) Units are tagged as excitatory or inhibitory based on monosynaptic peaks/troughs in the cross-correlation histogram ($p < 0.001$, convolution method; Stark and Abeles, 2009) and/or locally delivered 50–70 ms light pulses ($p < 0.001$, Poisson test; PV animals only). Nontagged units (692 of 1,413, 51%) are classified as putative pyramidal cells (PYR) or interneurons (INT) according to waveform morphology; nontagged units with low classification confidence ($p > 0.05$, n = 22, 1.6%) are not analyzed ("unclassified").

(C) Effect of single-shank pulses on locally recorded and distant cells (≥200 μm; n = 4 CaMKII mice, 8 PV mice). Intensities are scaled by the level used to induce the largest number of directly activated units per shank (the "optimal" DC intensity). Mean intensities at the center of the illuminated shanks were 0.56 (CaMKII) and 1.1 mW/mm^2 (PV). Bars below are group means (SEM) for the optimal intensity, and bars at the left refer to the local shank. CaMKII activation induces local spiking of PYR at a higher gain (bottom; defined as the firing rate during DC pulses divided by baseline firing rate, in the lack of light) than INT, whereas PV activation induces only localized INT spiking.

See also Figure S1.

(CaMKII::ChR2; n = 4 mice) or in the parvalbumin class of inhibitory interneurons (PV::ChR2; n = 8 mice) were used (Figure 1A). Animals were chronically implanted with multishank diode probes that enable independent light stimulation of small local groups of neurons while concurrently recording the extracellular spiking activity of directly and indirectly activated cells (Stark et al., 2012). Cells were classified as putative pyramidal cells (PYR) or interneurons based on monosynaptic connectivity, an increase in spiking during brief light pulses, and/or spike waveform features (Figure 1B, Figure S1 available online). Single-shank photostimulation with direct current (DC) pulses (50–70 ms) resulted in localized activation of targeted cells. At the "optimal" intensity (activating the largest number of targeted units per shank), 33% (101/309) of locally stimulated PYR were activated ($p < 0.05$; Poisson test) in CaMKII::ChR2 mice, whereas in PV::ChR2 animals, 59% (108/184) of locally stimulated interneurons were activated (Figure 1C) and these are referred to as PV cells throughout this paper. The abbreviation INT refers to physiologically identified putative interneurons that were not driven during PV photostimulation (a subset of INT may be PV cells that were not activated by light). Other (nonlocal and/or nontargeted) cells were weakly activated (e.g., INT recorded in CaMKII::ChR2 mice; Figure 1C, left) or not activated (e.g., local PYR recorded in PV::ChR2; Figure 1C, right). These findings illustrate effective spatiotemporal control of specific cell types in freely moving mice.

Selective stimulation of PYR with a time-varying chirp pattern (linear 0–40 Hz, 10 s; Figure 2A, bottom) induced spiking ($p < 0.05$; permutation test) at various frequencies with similar probabilities ($p = 0.41$, χ^2 test) in single PYR (121/257, 47%) and INT (27/46, 59%) in both hippocampus and neocortex (Figures 2A and 2C, left). Neurons typically spiked near the stimulus peak (at maximum light intensity/zero phase; Figure 2C, left; Figure S2A) but with slight phase shifts at progressively higher frequencies of the chirp (Figure 2C, bottom left; PYR: linear model, $\Phi(f) = -0.1 + 0.03f$; mean R^2 over n = 121 cells: 0.7; INT: $\Phi(f) = 0.29 + 0.02f$; $R^2 = 0.57$, n = 27; Figure 2D; Figure S2). Thus, PYR preceded INT spiking with a frequency-dependent delay, which was likely brought about by the kinetics of ChR2 (Boyden et al., 2005) and/or differential spike-generating mechanisms. Although individual PYR tended to spike at narrow frequency bands, this band differed from cell to cell and, at the group level, spanned the entire range of tested frequencies ($p = 0.44$; Kolmogorov-Smirnov test with a uniform null; Figure 2C, left; Figure S2B).

Chirp-pattern photostimulation of PV interneurons often induced high firing rates (mean ± SEM 142 ± 13 spikes/sec, n = 52 frequency modulated PV; Figure S2D) and wide-band spiking in these directly stimulated cells (Figure 2Bd), compared with just one or two spikes per cycle typically emitted during direct PYR stimulation (compare the left and right traces in Figure 2A). Overall, 60% of the tested interneurons (52/86) showed