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Role of Hippocampal CA2 Region in Triggering Sharp-Wave Ripples

Highlights

- Synchronous activity in CA2 region precedes sharp-wave ripples (SPW-Rs).
- Activity of deep CA2 pyramidal cells ramps up before SPW-R, then quickly drops
- Superficial CA2 cells fire synchronously preceding CA3 and CA1 during SPW-Rs
- CA2 cells contribute more strongly to WAKE SPW-Rs while CA3 participates more in SLEEP

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In Brief

Oliva et al. show that sharp-wave ripple (SPW-R) related activation of CA2 neurons precede those in CA3 and CA1. Deep CA2 cells gradually increase their activity prior to SPW-Rs, establishing the CA2 region as a potential trigger for SPW-R generation.

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Role of Hippocampal CA2 Region in Triggering Sharp-Wave Ripples

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SUMMARY

Sharp-wave ripples (SPW-Rs) in the hippocampus are implied in memory consolidation, as shown by observational and interventional experiments. However, the mechanism of their generation remains unclear. Using two-dimensional silicon probe arrays, we investigated the propagation of SPW-Rs across the hippocampal CA1, CA2, and CA3 subregions. Synchronous activation of CA2 ensembles preceded SPW-R-related population activity in CA3 and CA1 regions. Deep CA2 neurons gradually increased their activity prior to ripples and were suppressed during the population bursts of CA3-CA1 neurons (ramping cells). Activity of superficial CA2 cells preceded the activity surge in CA3-CA1 (phasic cells). The trigger role of the CA2 region in SPW-R was more pronounced during waking than sleeping. These results point to the CA2 region as an initiation zone for SPW-Rs.

INTRODUCTION

The functioning of the hippocampus is believed to depend on the unique contributions of its subregions and their interactions (Amaral and Lavenex, 2006). Hippocampus proper is made up by divisions of the *cornu Ammonis*, CA1, CA2, and CA3, each with specialized cell types and connectivity (Lorente de Nó, 1947). The vulnerability or resistance of the CA2 region stands out in several pathological conditions, including Alzheimer's disease (Braak et al., 1980), ischemia (Kirino, 1982; Sadowski et al., 1999), hippocampal sclerosis (Babb et al., 1984; Dam, 1980; Gloor, 1991; Kotloski et al., 2002; Sloviter, 1989) and schizophrenia (Benes et al., 1998; Knable et al., 2004; Narr et al., 2004; Nullmeier et al., 2011; Piskorowski et al., 2016; Zhang and Reynolds, 2002). CA3 but not CA2 neurons rapidly degenerate in kainic acid-induced status epilepticus (Nadler et al., 1978). The CA2 region can be clearly delineated from its neighboring regions by expression patterns of several peptides and genes (Kohara et al., 2014; Lein et al., 2004; Young et al., 2006).

Despite these distinct pathophysiological differences, the CA2 region has been traditionally considered as a transition zone, since its pyramidal neurons resemble CA3 neurons both in size and dendritic branching patterns (Ishizuka et al., 1995; Woodhams et al., 1993) and receive inputs from CA3 neurons, similarly to CA1 pyramidal cells (Lorente de Nó, 1947). They also receive input from dentate gyrus granule cells, but they lack the thorny excrescences characteristic of the CA3 neurons (Kohara et al., 2014). In addition to local inputs, CA2 interneurons receive excitation from CA1, CA3, the supramamillary body, and the amygdala (Bartesaghi et al., 2006; Benes and Berretta, 2001; Chevaleyre and Siegelbaum, 2010; Cui et al., 2013; Ding et al., 2010; Kohara et al., 2014; Maglóczky et al., 1994; Mercer et al., 2012; Piskorowski and Chevaleyre, 2012, 2013) and form a loop with layer II entorhinal neurons (Chevaleyre and Siegelbaum, 2010; Rowland and Moser, 2013). In addition to these anatomical differences, recent studies have pointed out the special cognitive and behavioral functions of the CA2 region (Dudek et al., 2016), including its postulated role in social recognition (Alexander et al., 2016; Hitti and Siegelbaum, 2014; Piskorowski et al., 2016; Smith et al., 2016), contextual memory (Alexander et al., 2016; Wintzer et al., 2014), and temporal coding (Mankin et al., 2015).

The hippocampus plays a prominent role in memory consolidation, and hippocampal sharp-wave ripples (SPW-Rs) represent a mechanism of memory transfer from the hippocampus to the neocortex (Buzsáki, 2015; Ego-Stengel and Wilson, 2010; Girardeau et al., 2009; Jadhav et al., 2012). SPW-R complex consists of two components: the sharp wave (SPW) and the ripple. The LFP sharp wave is a negative deflection that reflects the depolarization of the apical dendrites of CA1 pyramidal cells brought about by the synchronous discharge of the CA3 axonal input to those dendrites (Buzsáki et al., 1983; Fernández-Ruiz et al., 2012; Sullivan et al., 2011). On the other hand, the ripple is a ~140 Hz oscillatory event confined to the pyramidal cell body layer and represents a network response of CA1 pyramidal cells and interneurons to the strong synchronous drive (Buzsáki et al., 1992; English et al., 2014; Stark et al., 2014). While the CA3 region is implicated in the generation of the SPW, it is not homogenous in terms of its output pathways and the induction of SPW population bursts (Csicsvari et al., 2000; Mann and Paulsen, 2007). Specifically, whereas pyramidal cells in the CA3a (adjacent to CA2) and distal CA3b subregions give rise to extensive recurrent collaterals that are confined largely to the CA3 region and contribute to the creation of population events, more