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Increased Prevalence of Calcium Transients across the Dendritic Arbor during Place Field Formation

Highlights

- Virtual reality and functional microscopy used to study place field formation
- Local dendritic spikes are likely first events in forming many new place fields
- Release of dendritic inhibition creates plasticity window during novel experiences
- Synaptic plasticity in place cells implicated in forming new place fields

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In Brief

Sheffield et al. reveal microscopic plasticity-related events occurring in hippocampal neurons that likely underlie spatial memory formation when animals encounter new environments.

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Increased Prevalence of Calcium Transients across the Dendritic Arbor during Place Field Formation

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SUMMARY

Hippocampal place cell ensembles form a cognitive map of space during exposure to novel environments. However, surprisingly little evidence exists to support the idea that synaptic plasticity in place cells is involved in forming new place fields. Here we used high-resolution functional imaging to determine the signaling patterns in CA1 soma, dendrites, and axons associated with place field formation when mice are exposed to novel virtual environments. We found that putative local dendritic spikes often occur prior to somatic place field firing. Subsequently, the first occurrence of somatic place field firing was associated with widespread regenerative dendritic events, which decreased in prevalence with increased novel environment experience. This transient increase in regenerative events was likely facilitated by a reduction in dendritic inhibition. Since regenerative dendritic events can provide the depolarization necessary for Hebbian potentiation, these results suggest that activity-dependent synaptic plasticity underlies the formation of many CA1 place fields.

INTRODUCTION

The hippocampus is critical for the formation and storage of spatial memories (Morris et al., 1982; Teng and Squire, 1999). Hippocampal place cells not only fire when animals move through a particular location (place field) (O'Keefe and Dostrovsky, 1971), but during sleep and rest subsequent to the experience they can reactivate in the same (or reverse) sequence as during the experience (Carr et al., 2011; Foster and Wilson, 2006; Sadowski et al., 2016; van de Ven et al., 2016; Wilson and McNaughton, 1994). This has led to the idea that place cell ensembles represent a cognitive map of space and a memory of places. Hippocampal pyramidal neurons, which are the cells that form place fields during spatial navigation, are capable of engaging activity-dependent Hebbian synaptic plasticity (Bliss and Collingridge, 1993), a potential mechanism by which spatial information can be encoded and stored. Indeed, disruption of components of the molecular pathways involved in synaptic plasticity, such as NMDA receptors or CaMKII, is correlated with behavioral deficits in memory or spatial navigation tasks (Morris et al., 1986; Silva et al., 1992; Tsien et al., 1996). Given that ensembles of place fields are thought to represent spatial memories and are likely used for spatial navigation, these findings have led to the hypothesis that place fields may form *de novo* through activity-dependent synaptic plasticity (Takeuchi et al., 2013), with some evidence supporting this view (Bittner et al., 2015; Monaco et al., 2014). However, there is significant evidence supporting an alternative view, that synaptic plasticity may not be required for place field formation (Cacucci et al., 2007; Dragoi and Tonegawa, 2011, 2013a; Frank et al., 2004; Hill, 1978; Kentros et al., 1998; McHugh et al., 1996). For example, after hippocampal synaptic plasticity is perturbed or blocked, place fields are typically less precise (Cacucci et al., 2007; Kentros et al., 1998; McHugh et al., 1996; Rotenberg et al., 1996), less stable (Kentros et al., 1998; Rotenberg et al., 1996), and fail to shift backward (Ekstrom et al., 2001), but nonetheless place fields still form. Additionally, many place fields are immediately present upon the animal's first traversal across a novel environment (Frank et al., 2004; Hill, 1978). Such a rapidly appearing cognitive map suggests that hippocampal representations could arise through the novel stimulus-dependent selection of pre-strengthened neuronal ensembles (Deguchi et al., 2011; Dragoi and Tonegawa, 2011, 2013a, 2013b; Lee et al., 2012). These results call into question the idea that place fields form *de novo* through synaptic plasticity during experience of a novel environment.

It has been difficult to assess directly the involvement of synaptic plasticity in awake animals engaged in navigation tasks. One step toward this goal would be to investigate dendritic regenerative events (back propagating action potentials or dendritically generated spikes, here collectively referred to as branch spikes [Sheffield and Dombeck, 2015]), which are thought to provide the post-synaptic depolarization necessary for Hebbian potentiation when paired with presynaptic input (Golding et al., 2002; Magee and Johnston, 1997; Schiller et al., 1998). Measuring the occurrence of branch spikes during place field formation would therefore indicate periods in which Hebbian synaptic potentiation could be occurring. A recent