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Dendritic mechanisms of hippocampal place field formation

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Place cells in the hippocampus are thought to form a cognitive map of space and a memory of places. How this map forms when animals are exposed to novel environments has been the subject of a great deal of research. Numerous technical advances over the past decade greatly increased our understanding of the precise mechanisms underlying place field formation. In particular, it is now possible to connect cellular and circuit mechanisms of integration, firing, and plasticity discovered in brain slices, to processes taking place *in vivo* as animals learn and encode novel environments. Here, we focus on recent results and describe the dendritic mechanisms most likely responsible for the formation of place fields. We also discuss key open questions that are likely to be answered in the coming years.

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Introduction

Place cells are a subset of the excitatory pyramidal neurons in the hippocampus that fire at specific locations within an animal's local environment (place field) [1]. Ensembles of place cells tile the environment with place fields, with orthogonal ensembles encoding different environments. During sleep and wakeful rest, place cells can reactivate in the same (or reverse) sequence as during the preceding experience [2–6], leading to the idea that orthogonal place cell ensembles represent distinct maps of different environments, and a cellular substrate of spatial memory.

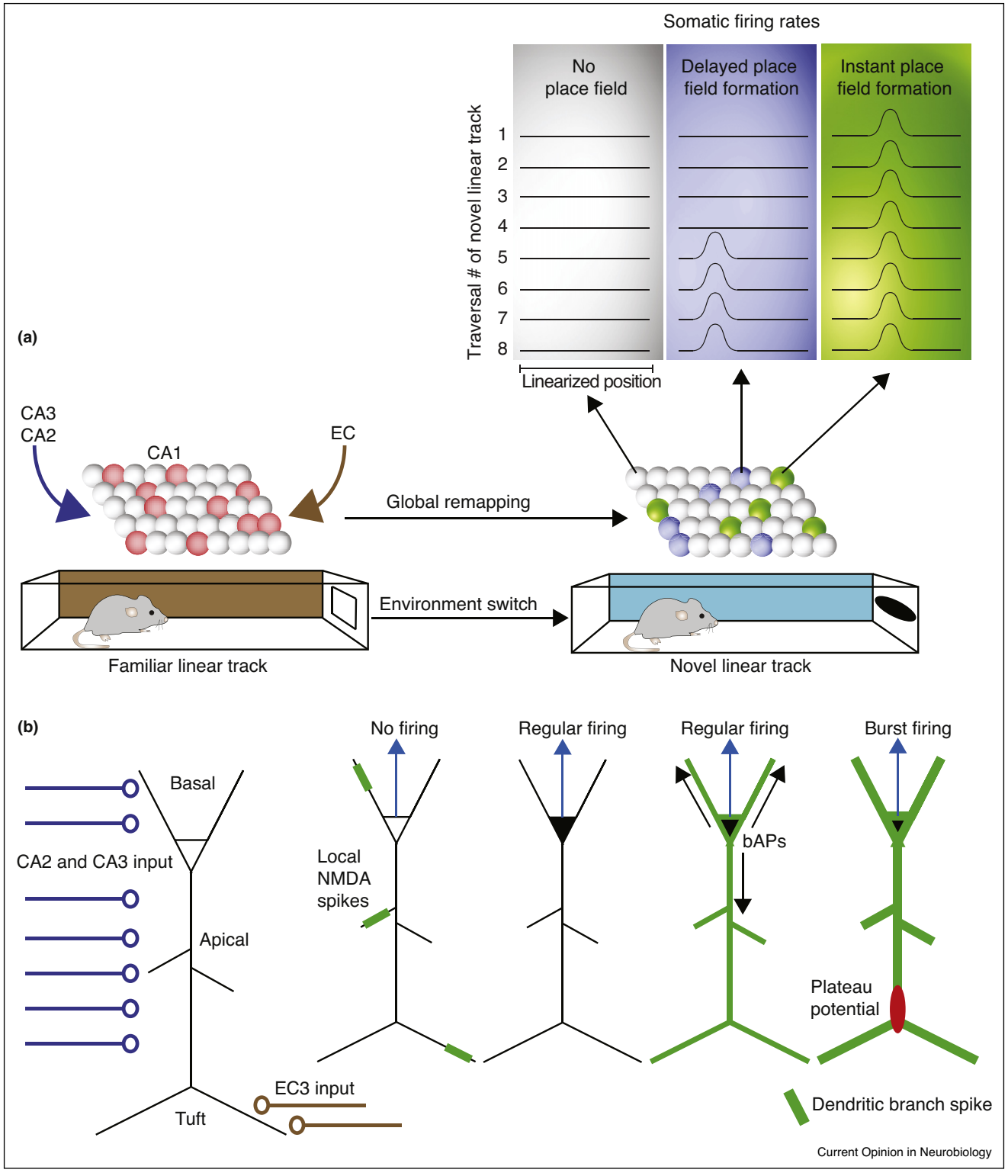
Here we focus on the cellular and circuit mechanisms that contribute to the formation of new place fields in the CA1 region of the hippocampus when animals are exposed to novel environments (Figure 1). The mechanisms underlying place field and spatial memory formation may generalize to other types of memories encoded in the hippocampus (contextual fear, trace, etc.) [7,8], thus revealing general principles of hippocampal memory formation.

When animals navigate in a familiar environment, ~25% of CA1 neurons display place field firing [9,10]. When animals are switched to a novel environment, 'global remapping' takes place, where a random ~25% of neurons across the population encode the novel environment [11,12•,13–16,17•]. The identity of these cells cannot be predicted based on the cells encoding the familiar environment. Further, if two place cells each have a place field in both environments, the location of these place fields with respect to one another in the environments is also unpredictable. Nevertheless, 3 general functional cell types appear in the novel environment that together form the new map (Figure 1a) [17•,18,19,20•]: first, instant place cells that begin somatic action potential (AP) firing in the place field the first time the animal traverses the field location, second, delayed-onset place cells that begin somatic AP firing in the place field only after the animal traverses the field location multiple times, and third, silent cells that rarely fire somatic APs. Here we treat each functional cell type (instant, delayed and silent, Figure 1a) separately, and describe the mechanisms most likely responsible for their formation. We will also discuss dendritic mechanisms that may determine the precision and stability of place fields after formation.

Regenerative dendritic events and plasticity

Hippocampal pyramidal neurons can engage activity-dependent synaptic plasticity [21], a mechanism by which spatial information could be encoded and stored [22–24]. NMDA-dependent potentiation requires presynaptic glutamate release paired with a post-synaptic regenerative dendritic event (strong depolarization in the dendrites, here referred to as 'branch spikes' [25•]) to relieve NMDA channel magnesium block and allow for a large influx of calcium to activate enzymatic plasticity pathways. Brain slice research has revealed numerous types of branch spikes, such as all-pervasive back-propagating APs (bAPs) originating in the soma or axon initial segment [23,26–28], partially invasive bAPs [23,27], plateau potentials [29•,30•,31] and local NMDA spikes (local branch spikes) [32–36] (Figure 1b). These distinct branch spikes are caused by varying engagement of distinct types of

Figure 1



Hippocampal place field formation at the ensemble level and active dendritic signaling in CA1 pyramidal neurons. **(a)** Switching from a familiar to a novel environment causes global remapping of CA1 place fields (colored neurons indicate place cells). CA1 neurons in the novel environment can either be silent (no place field), form a place field after some time or experience (delayed place field), or form a place field immediately (instant place field). **(b)** CA1 pyramidal neurons receive input from CA2 and CA3 on their basal and proximal apical dendrites, and entorhinal layer 3 cortical inputs on their tuft dendrites (Left). These inputs can cause a number of postsynaptic responses (from left to right): local NMDA spikes