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Place cells and long-term potentiation in the hippocampus

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ABSTRACT

Place cells show location-specific firing patterns according to an animal's position in an environment and are thought to contribute to the spatial representation required for self-navigation. Decades of study have extensively characterized the properties of place cells and suggested the involvement of long-term potentiation (LTP), a long-lasting synaptic strengthening, in place cell activity. Here, we review the basic characteristics of place cell activity and the findings that support the idea that LTP contributes to the formation, maintenance, and plasticity of place cell activity.

1. Introduction

Our brains are able to provide us with a sense of our own position in an environment, a process that is thought to be mediated by the hippocampus. O'Keefe and Dostrovsky (1971), using a set of implanted microelectrodes in rat brains, discovered that neurons in the hippocampus exhibit firing in some specific locations but not in others within an environment. These neurons with location-specific firing patterns were later named "place cells" (O'Keefe, 1979). Place cells have been most extensively studied in rats and mice, but they are also found in the human hippocampus (Ekstrom et al., 2003).

2. Place cells in the hippocampus

Place cells are hippocampal neurons that fire at a high frequency when an animal visits a specific region of an environment (Fig. 1A). Each place cell has its own preferred firing region, commonly known as a place field. Different place cells have place fields in different regions of an environment. Some place cells fire in response to the combination of an animal's position and certain other factors (e.g., sensory stimuli, behavior), whereas others appear to fire based solely on an animal's position, regardless of other factors (Muller, Kubie, & Ranck, 1987; O'Keefe, 1976). Place cells have been identified in all hippocampal subregions, the CA1-3 areas (Leutgeb, Leutgeb, Treves, Moser, & Moser, 2004; Lu, Igarashi, Witter, Moser, & Moser, 2015; Mankin, Diehl, Sparks, Leutgeb, & Leutgeb, 2015; McNaughton, Barnes, Meltzer, & Sutherland, 1989; O'Keefe and Dostrovsky, 1971; Park, Dvorak, & Fenton, 2011) and the dentate gyrus (Alme et al., 2010; Jung & McNaughton, 1993; Neunuebel & Knierim, 2012). In the CA1 area, pyramidal cells have been shown to exhibit place cell activity (Bittner et al., 2015; Dombeck, Harvey, Tian, Looger, & Tank, 2010; Fox & Ranck, 1975, 1981; Henze et al., 2000). However, the identity of place cells in the dentate gyrus has been controversial. Different cell types, such as granule cells, young granule cells and mossy cells, have been proposed to exhibit place cell activity (Alme et al., 2010; Danielson et al., 2016; Jung & McNaughton, 1993; Neunuebel & Knierim, 2012). In addition to these place cells in the hippocampus, other cell types in brain regions outside the hippocampus have been reported to show spatially modulated fir-

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Abbreviations: LTP, Long-term potentiation; CA1, Cornu Ammonis area 1; CA3, Cornu Ammonis area 3; NMDA receptor, N-methyl-D-aspartate receptor; CaMKIIα, calcium/calmodulin-dependent protein kinase type II alpha; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; ERK, extracellular-signal-regulated kinases; CREB, cAMP response element-binding protein; PKMζ, protein kinase Mζ; AMPA receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NR1, glutamate ionotropic receptor NMDA type subunit 1; GluR1, glutamate ionotropic receptor AMPA type subunit 1; CPP, (±)-3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid; ZIP, Zeta Inhibitory Polypeptide.

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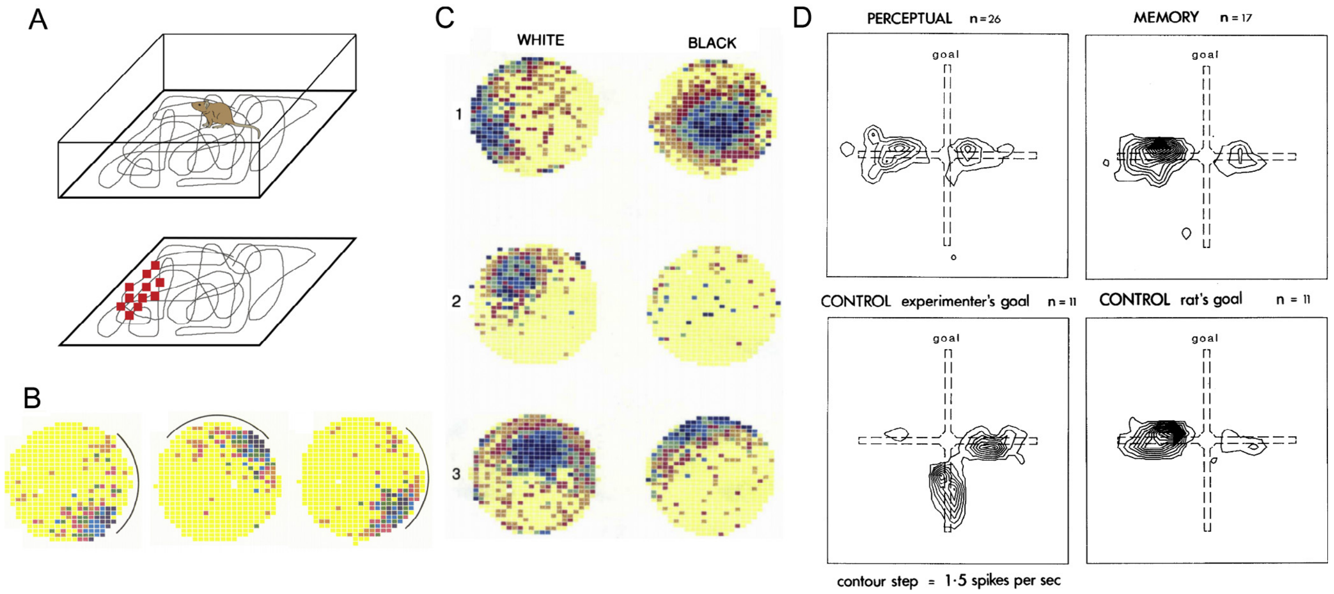

Fig. 1. Characteristics of place cell activity. (A) A schematic illustrating a typical experiment in a square enclosure. The top image shows the animal's trajectory as a gray line, while the bottom image uses red dots to represent the locations of place cell firing. (B) Color-coded rate maps for a place cell recorded while a rat explored a cylindrical enclosure with a cue card placed on its wall (shown by a curved line). Three recording sessions were performed when the cue card was placed at the 3 O'clock (left), 12 O'clock (middle) and then 3 O'clock (right) positions. Between each session, the cue card was moved while the rat was taken out of the enclosure. Note that the movement of the place field followed the movement of the cue card. In B and C, blueish colors represent high firing rates, while yellowish colors indicate low rates. Republished with permission of Society for Neuroscience, from Muller and Kubie (1987); permission conveyed through Copyright Clearance Center, Inc. (C) Color-coded rate maps show the "remapping" of three place cells (cell 1, 2, and 3). These cells were recorded in a cylindrical enclosure with either a white (left side) or black (right side) cue card. Note that the location of the place fields changed depending on which card was placed. In the case of cell 2, the place field disappeared when the black card was used. Reproduced from Bostock, Muller, and Kubie (1991) with permission of John Wiley and Sons. (D) The contour plots show the firing rate of a place cell recorded from a rat in a four-arm maze. In this experiment, the rat was trained to navigate to a goal arm position relative to visual spatial cues. The four panels show rate maps recorded under different conditions. "Perceptual" indicates recording sessions in the presence of visual spatial cues. "Memory" indicates recording sessions after the visual cues were removed in the presence of the rat in the maze. Note that spatial firing patterns are similar between the perceptual and memory periods. "Control" indicates recording sessions where the rat was introduced into the maze in the absence of visual cues. "Experimenter's goal" shows a rate map formed relative to a goal arm arbitrarily chosen by the experimenter, while "rat's goal" represents a rate map formed relative to a goal arm chosen by the rat. Note that the "rat's goal" map shows a similar pattern to the perceptual and memory maps. Reproduced from O'Keefe and Speakman (1987) with permission of Springer. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ing patterns, such as head direction cells in the presubiculum and other areas (Taube, 2007) and grid cells in the medial entorhinal cortex (Rowland, Roudi, Moser, & Moser, 2016).

3. Characteristics of place cell activity

3.1. Visual information exerts strong control over the position of place fields

Studies have shown that place cell activity is strongly controlled by the visual information that animals receive from the surrounding environment. Muller and Kubie (1987) tested whether place cell activity is influenced by the position of a visual landmark in the form of a white cue card placed on the wall of a cylindrical enclosure. They found that when the cue card was moved by 90° steps along the cylindrical wall, the positions of the place fields followed the rotation of the cue card position (Fig. 1B). Similarly, O'Keefe and Speakman (1987) moved all spatial cues in an experimental room together by 90° steps around the center of a four-arm maze and found that the place fields of many place cells followed the rotation of the spatial cues. Thus, visual information plays a critical role in determining the positions of place fields.

3.2. Place fields are determined by multiple types of sensory information

Although visual information was found to play a critical role under some conditions, as described above, Quirk, Muller, and Kubie (1990) showed that place cells are able to maintain constant spatial firing patterns even in the dark. Furthermore, a study using blind rats indicated the existence of place fields in the complete absence of visual input (Save, Cressant, Thinus-Blanc, & Poucet, 1998), suggesting that place cells do not rely solely on visual information to generate their location-specific firing patterns. Olfactory (Zhang & Manahan-Vaughan, 2015) and tactile inputs (Gener, Perez-Mendez, & Sanchez-Vives, 2013) have also been shown to help determine the locations of place fields. Thus, the location specificity of place cell firing is not determined by any specific sensory modality but by the integration of multiple types of sensory information, although a particular sensory modality can be dominant depending on the nature of the surrounding environment.

3.3. Remapping between environments

When an animal is exposed to two different environments, what happens to place cells? Studies have shown that some place cells with place fields in one environment had no place field in another environment (Muller & Kubie, 1987; O'Keefe and Conway, 1978; Thompson & Best, 1989). Other place cells were found to be active in multiple environments; however, the positions of their place fields seemed to change randomly between environments (Muller & Kubie, 1987) (Fig. 1C). Place cells whose place fields are at the center of one environment had place fields either at the center or in the periphery of another environment. Thus, different groups of place cells become active in different environments, and the positions of their place fields do not show any predictable relationship between environments. Muller and Kubie termed this phenomenon "remapping".