Synaptic plasticity supports slow gamma phase-locking in CA1 place cells during environmental novelty

Vincent Douchamps\textsuperscript{1,2}, Ayumu Tashiro\textsuperscript{1,2}

\textsuperscript{1}Warwick-NTU Neuroscience Programme, School of Biological Sciences, Nanyang Technological University, Singapore, 138673, Singapore

\textsuperscript{2}Warwick-NTU Neuroscience Programme, School of Life Sciences, University of Warwick, Coventry, CV4 7AL, UK

Correspondence: Vincent Douchamps
E-mail: vincent.douchamps@gmail.com
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Information processing and transfer between brain structures have been proposed to engage the phase-locking of neuronal firing to gamma oscillations during certain cognitive functions, including learning and memory. The cellular mechanism behind this precise temporal organisation of action potentials might rely on changes in synaptic strength. Kitanishi \textit{et al.} (Kitanishi T, Ujita S, Fallahnezhad M, Kitanishi N, Ikegaya Y, Tashiro A. Neuron, 86:1265-76, 2015) tested this hypothesis by blocking synaptic plasticity dependent on the GluR1 subunit of AMPA (\textit{\alpha}-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor using a virus-mediated local genetic manipulation in a restricted population of CA1 principal cells. Multi-tetrode-based unit recording from these genetically-modified principal cells showed that environmental novelty was associated with an impaired phase-locking to slow gamma oscillations and a slower emergence of precise spatial firing compared to control cells. This pattern of deficits suggests that CA3-driven slow gamma oscillations might induce GluR1-dependent synaptic plasticity in CA1. This cellular mechanism would in turn participate in the rapid emergence of precise place fields in CA1 during novel experiences, and in the transfer of this information to downstream neurons in a temporally-organised manner.

Keywords: GluR1; synaptic plasticity; gamma oscillations; phase locking; place cells; CA1

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Gamma oscillations, present in the hippocampo-entorhinal system\textsuperscript{[1]}, have been associated with information processing related to learning and memory\textsuperscript{[2]}. Notably, phase-locking to gamma oscillations, that is, the temporal alignment of neuronal firing to specific phases of these oscillations, would facilitate the transfer of information to downstream structures because such synchronized firing is more likely to be impactful. The cellular mechanism underlying gamma phase-locking is not well-understood; it is believed to rely on the balance between excitatory and inhibitory inputs\textsuperscript{[1]}. To investigate this question, Kitanishi and colleagues\textsuperscript{[3]} blocked long-term potentiation (LTP) and recorded the neuronal activity during environmental novelty, when the excitation-inhibition balance is expected to be altered following learning-related synaptic changes. Importantly, this blockade of LTP had to be restricted to a small neuronal population in order to exclude brain-wide alterations, a frequent caveat of more traditional techniques based on
pharmacological agents and transgenic animals. For this reason, the authors devised a new approach using a virus-mediated local genetic manipulation in a restricted population of neurons, combined with local chronic implantation of electrodes to record extracellular unit activity in freely-moving rats. The aim was to study the role of GluR1-dependent synaptic plasticity in regulating the firing patterns of CA1 principal cells.

**Isolation of postsynaptic cellular mechanisms by local genetic manipulation**

Kitanishi et al. [3] injected a small amount of recombinant adeno-associated viral vectors in a minor portion within dorsal CA1 of rats to spatially restrict the manipulation although enough to ensure that recording electrodes could be inserted reliably within the infected area. In one hemisphere, the vector expressed GFP-GluR1-c-tail under the control of the CaMKII promoter. The GFP was used to confirm that the recording electrodes were situated within the infected area. The GluR1 gene encodes a subunit of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, and the GluR1-c-tail is its dominant-negative mutant, which suppresses forms of LTP by interfering with the synaptic delivery of GluR1-containing AMPA receptors [4, 5]. Kitanishi et al. [3] showed that GluR1-c-tail blocks Schaffer collaterals-CA1 LTP induced by theta burst stimulation in brain slices while it did not alter the basal synaptic transmission [4-6]. Finally, the CaMKII promoter allowed to target specifically the pyramidal cells.

A control vector that contains the GFP gene but not the GluR1-c-tail was injected at the equivalent position in the contralateral hemisphere. Single-cell and local field potential recordings were bilaterally made from the virus-infected areas. This within-animal control reduces difficulties of interpretation caused by differential behaviour, which is inevitable when control and experimental recordings are performed in different animals. For example, it is important to control for running speed because it can affect theta and gamma oscillations [7, 8] or the influence of CA3 input over CA1 firing activity [9]. Furthermore, the cognitive, motivational and behavioural brain functions should be mostly preserved with this method given the genetic manipulation leaves intact the upstream and downstream areas, as well as most of the target structure. The observed effects should thus be attributable to the local cellular mechanisms, but not to an altered input. Hence, comparing the electrophysiological activity between the GluR1-c-tail and control hemispheres should reveal the role of the GluR1-dependent synaptic plasticity.

**Rapid formation of spatial representation relies on GluR1-dependent synaptic plasticity**

Pyramidal neurons in dorsal CA1 were targeted because they display a location-specific firing pattern while an animal explores an environment. Those neurons are often referred to as ‘place cells’ [10]; each place cell tends to discharge only when the animal occupies a specific location, remaining silent otherwise. This spatial firing can be stable across multiples days and is not driven purely by sensory information [11], supporting their involvement in memory. Importantly, these spatial firing patterns can appear rapidly [12, 13] when the animal is placed in a novel environment and possibly establish a new environmental representation. For this reason, understanding the mechanisms underlying place cells activity may provide valuable insights into memory formation.

Kitanishi et al. [3] found that, when the rats were exposed to environmental novelty, CA1 principal cells in the GluR1-c-tail-expressing hemispheres were able to show location-specific firing patterns. However, their place fields emerged with a 2-min delay and were larger than for control cells during the first 10-min novelty session. Repeated exposure to the once-novel environment abolished this difference, so that place field properties were comparable in both hemispheres. This temporal pattern of spatial deficits is similar to a previous study in which CA3 projections to CA1 were silenced [14]. Another system, likely the entorhinal cortex-CA1 system [15], may thus mediate a slower acquisition of sharp CA1 place fields, independently of GluR1-dependent synaptic plasticity. Although not mandatory, the CA3-CA1 system would allow faster encoding by quickly inducing GluR1-dependent synaptic plasticity within CA1.

**Informational transfer based on slow gamma phase-locking relies on GluR1-dependent synaptic plasticity**

In parallel to the spatial deficit during novelty, GluR1-c-tail principal cells in CA1 showed an impaired phase-locking of their firing to local slow gamma oscillations (25-50 Hz). On the other hand, these oscillations increased in power in an extent comparable to those in the control hemisphere. The power of slow gamma oscillations in the local field potential is thought to reflect the strength of incoming input of CA3 onto CA1 while the phase-locking of firing to such oscillations indicates how the output activity of a neuron temporally aligns to the oscillations [16, 17]. Thus, inputs were presumably unaffected by the genetic manipulation, as expected from its local nature, but GluR1-c-tail principal cells were not able to synchronise their firing with inputs reaching them at slow gamma
frequency. Interestingly, slow gamma oscillations in CA1 local field potential would represent a preferential communication between CA1 and CA3 [16, 17]. This impaired phase-locking to slow gamma oscillations thus suggests that GluR1-dependent plasticity may be involved in the processing of incoming CA3 information within CA1 principal cells during novelty. This lower synchrony of firing could in turn impede the transfer of this information downstream of CA1 because synchronized spikes are more likely to influence receiving neurons [22].

In contrast, fast gamma oscillations (65-140 Hz) and phase-locking to them were intact. Given fast gamma rhythm is associated with an enhanced informational flow from the layer III of the entorhinal cortex (EC3) [16], the processing within the entorhinal-CA1 system might not be crucially conditioned by GluR1-dependent synaptic plasticity. This is in line with the lower density of GluR1-containing AMPA receptors on the distal rather than proximal dendrites of CA1 principal cells, which are innervated by EC3 and CA3 projections respectively [18]. On the other hand, the finding was somewhat surprising because the association of fast gamma oscillations with memory encoding has been suggested previously [16]. Maybe some deficit would be revealed by splitting the fast gamma frequency band further into two sub-bands, which are recently suggested to be mediated by different mechanisms [19, 20].

Recent studies have suggested that dendritic plateau potentials contribute to the integration of CA3 and EC3 inputs and generate place cell activity in CA1 pyramidal neurons [21, 22]. Dendritic plateau potential is a long-lasting dendritic membrane depolarization dependent on voltage-gated Ca²⁺ channels and N-methyl-D-aspartate receptors. The CA3 input into the proximal dendrites depolarizes dendrites maybe via back-propagated action potentials. EC3 input can interact with this depolarization to generate dendritic plateau potentials. The generation of dendritic plateau potentials seems to precede the place field formation [21, 22] and can contribute to synaptic plasticity [23, 24]. Therefore, delayed development of place field firing in GluR1-c-tail place cells in CA1 might be caused by impaired synaptic plasticity which depends on both the synaptic delivery of GluR1-containing AMPA receptor and the generation of dendritic plateau potentials. The mechanistic relationship among GluR1-dependent synaptic plasticity, slow gamma phase-locking and dendritic plateau potentials may be key information to understand cellular mechanisms underlying the generation of place cell activity.

Conclusions

Kitanishi et al. [3] introduced a new method combining local genetic manipulation and electrophysiological recording to investigate the function of cellular mechanisms. Following local virus-mediated expression of GluR1-c-tail to suppress GluR1-dependent LTP in a small population of CA1 principal cells, place cells firing was initially delayed, less precise and not phase-locked to slow gamma oscillations. GluR1-dependent synaptic plasticity might thus support the rapid emergence of some spatial and temporal firing patterns of CA1 pyramidal cells during environmental novelty. CA3-driven slow gamma oscillations would especially contribute to the induction or early-phase of this form of LTP, as suggested by the early nature of the observed deficits. Overall, GluR1-dependent synaptic plasticity might control the flow of EC3 and CA3 information downstream of CA1, favouring CA3 inputs during the initial stages of memory formation. Additional studies are needed to shed more light on how the GluR1-dependent synaptic plasticity interacts with other cellular mechanism to establish place cell activity and function as the cellular basis of memory.

Conflicting interests

The authors have declared that no conflict of interests exist.

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Abbreviations

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; LTP: long-term potentiation.

Author contributions

V.D. and A.T. wrote the manuscript.

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