Mechanisms constraining inhibitory dynamics in hippocampal CA1

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Introduction

Information processing in the brain requires precise coordination across individual neuronal elements, allowing for a balance between excitatory (E) and inhibitory (I) activity. Inhibitory function is mediated by highly heterogeneous populations of GABAergic interneurons that control activity propagation within neuronal circuits. There exists a large breadth of these interneurons, and each class is functionally distinct. It is thought that the coordinated action of GABAergic interneurons relies on their timely recruitment during ongoing brain activity. However, the main synaptic and neuronal determinants gating interneuron recruitment remain generally unknown.

In most brain regions, GABAergic interneurons constrain excitatory activity through feedforward (FF) and feedback (FB) inhibition. These two circuit motifs are present within the hippocampus. The last excitatory relay of this temporal lobe structure consists of a CA4 to CA1 connection in which axons of CA3 pyramidal cells, termed Schaffer’s collaterals, project to CA1. In CA1, GABAergic interneurons can undergo direct or indirect recruitment, and some cells may even experience both. The direct excitation of interneurons in CA1 occurs via excitatory CA3–CA1 synapses, while the indirect excitation of CA1 interneurons involves their activation via cells in CA1, leading to the FB inhibition of pyramidal neurons in this region.

These circuit motifs have long been appreciated; however, how they segregate between different subtypes of interneurons remains obscure. Moreover, the main determinants constraining interneuron activity in either a FF or FB configuration has yet to be investigated.

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CA1 hippocampal INs are morphologically distinct

A, B, C recordings from CA1 INs following a single SC stimulus. PV+ perisomatic-targeting INs experience direct excitation while PV- bistriated INs undergo direct and indirect recruitment, and SST- OLM INs are not activated by a single SC stimulus. D, E Examples of PV+ perisomatic-targeting (right), bistriated (middle), and SST- OLM (left) INs used in these recordings.

Excitation motifs gate IN recruitment during repetitive activity

A. Examples of PV+ perisomatic-targeting (top), bistriated (middle), and OLM (bottom) INs used in these recordings. B, C PV+ and PV- INs exhibit indirect recruitment. D, E The relative timing of activation between IN subtypes remains constant with increasing stimulus number. There is a decrease in perisomatic-targeting and bistriated IN firing followed by an increase in OLM cell firing over time.

Hippocampal INs preserve their relative timing of activation

A. Recording scheme. B, C AP latency measurement. E, F Examples of PV+ perisomatic-targeting (top), bistriated (middle), and SST- OLM (left) INs. G, H The relative timing of activation between IN subtypes remains constant with increasing stimulus number. There is a decrease in perisomatic-targeting and bistriated IN firing followed by an increase in OLM cell firing over time.

Summary and Conclusion

We find that segregation of direct (CA3) and indirect (CA1) excitatory inputs contributes to the cell type-specific recruitment of these interneuron classes. PV+ perisomatic-targeting cells were recruited mainly via direct excitation, leading to FF inhibition, while SST- OLM cells were exclusively recruited by indirect excitation to execute FB inhibition. Interestingly, PV+ bistriated cells with axons terminating on the proximal dendrites of CA3 pyramidal neurons were excited by direct and indirect afferents. Thus, these interneurons map onto pyramidal cells along a spatial continuum, defined by direct and indirect recruitment. Notably, repetitive high-frequency SC stimulation led to cell type-specific changes in activity. Perisomatic-targeting interneurons decreased their firing probability during repetitive stimulation while OLM cells were initially silent but later increased their activity. Bistriated cells demonstrated an elevated firing probability, which gradually decreased. These results suggest that the recruitment of interneurons by direct and indirect afferents is precisely coordinated.