Recurrent Excitation Facilitates High-Conductance Network Events in the Mouse Neocortex

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Introduction

Most synapses impinging onto an individual pyramidal cell (PC) in the neocortex originate from nearby excitatory cells [2,4], signifying the importance of recurrent excitatory connections in cortical circuits. This connectivity scheme is exemplified in the barrel cortex of rodents, in which feedforward activation of a single barrel results in reverberant feedback activity in the superficial cortical layers that is spatially confined to a single cortical column [3]. We hypothesized that the amount of recurrent excitation directly correlates with the amount of network activity. To test this hypothesis, we used a mouse model in which the genetic ablation of the mitogen-activated protein kinase Erk2 results in reduced density of mature PCs within cortical layers 2/3 [in preparation]. The decrease in PC density should lead to a decrease in the number of local synaptic contacts, onto neighboring PCs, provided that the number of projections from the spared PCs is unaltered. We, thus, compared global network excitability in brain slices from wild-type and mutant mice in the form of high-conductance events (HCEs). A simple computer model exhibiting bistability can best account for the role of recurrent excitation in modulating network activity observed in experiments.

Methods

We used 350 µm thalamocortical slices [1] of somatosensory cortex from juvenile (P14-P21) C57BL/6 wild-types (WT) and Erk2 conditional knockout mice (cKO) in which expression of Erk2 was conditionally ablated within the dorsal telencephalon using an Emx1-cre during early embryonic development (E9). Voltage traces were obtained from layer 2/3 pyramidal cells (PCs) using single-cell patch clamp experiments in the current-clamp configuration. Network activity was increased with 5 µM gabazine, a GABAA receptor antagonist, to induce spontaneous network activity. To test for differences in HCEs between WTs and cKOs. In computer simulations, we performed for 10 minutes to quantify the frequency of disinhibition-induced HCEs from layer 2/3 PCs from somatosensory cortex or WT and cKO mice. A, B show raw voltage traces of HCEs as a proxy for network activity in WT and cKO animals, respectively. An individual HCE is characterized by a plateau depolarization of ~60 mV, lasting from the onset of each of the pairs of the plateau, after which depolarization block prevents further spiking (see Figure 3A). C, Quantification of number of HCEs over a 10-minute period. Crosses connected by a line demarcate the means of the distributions (WT: n = 35; cKO: n = 32; p = 0.05, non-parametric bootstrapping analysis).

Results

1. Deletion of Erk2 during early embryonic development results in decreased network excitability in layer 2/3 of somatosensory cortex in vitro

Figure 1: Cortical network activity recorded from single L2/3 PCs from somatosensory cortex or WT and cKO mice. A, B show raw voltage traces of HCEs as a proxy for network activity in WT and cKO animals, respectively. An individual HCE is characterized by a plateau depolarization of ~60 mV, lasting from the onset of each of the pairs of the plateau, after which depolarization block prevents further spiking (see Figure 3A). C, Quantification of number of HCEs over a 10-minute period. Crosses connected by a line demarcate the means of the distributions (WT: n = 35; cKO: n = 32; p = 0.05, non-parametric bootstrapping analysis).

2. HCE decay is altered in Erk2 cKO mice, while plateau remains unchanged

Figure 2: A. Average HCEs from WT and cKO mice. Individual HCEs traces were aligned relative to event onset and then averaged for the WT and cKO groups. Note the difference during the decay (tail) phase of the HCE. B, Quantification of the mean area of the HCE tail taken as the integral of the membrane voltage during the HCE tail (WT: n = 35; cKO: n = 32; p = 0.05, non-parametric bootstrapping analysis).

Conclusions

• Erk2 conditional knockout mice serve as an appropriate model to probe cortical excitability owing to their phenotype of having reduced cell density in cortical layers 2/3.
• The frequency of high-conductance events recorded in vitro from layer 2/3 cortical pyramidal cells in a disinhibited brain slice serves as a proxy for cortical network excitability.
• Erk2 cKO exhibit decreased network excitability and diminished excitatory feedback.
• A simple computational model of excitatory and inhibitory neuronal populations reproduces the decreased excitability phenotype observed experimentally when recurrent excitation is reduced.

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References

4.) Neocortex contains at least two levels (high and low) of recurrent excitation.

Figure 3: Quantification of recurrent excitation before and after HCE onset. A, Example trace of a single HCE from a layer 2/3 PC. Insets show excitatory postsynaptic potentials (EPSPs) demarcated by arrows during a 2-second period before HCE onset (Pre-HCE) and during a 2-second period after HCE onset (Post-HCE). B, Boyle of the EPSP count during the Pre- and Post-HCE periods in WT and cKO mice. Red crosses represent outliers. In both WTs and cKOs, a significant increase in the EPSP count is present after HCE onset, suggesting that increase in activity is due to activation of the local cortical network (WT: n = 33; cKO: n = 33; p = 0.01, non-parametric bootstrap analysis). WTs have significantly higher EPSP counts during the Pre- and Post-HCE period than cKOs, suggesting that cKOs have a reduced recurrent excitation.

Figure 4. A simple model of excitatory and inhibitory populations accounts for the experimental observations. We generated a two-dimensional model exhibiting bistable dynamics. One variable describes the activity of the excitatory population and the other of the inhibitory population. Activity is reported as a generic membrane potential of a neuron in each population. Unrelated noise added to both populations facilitates transitions from the low to the high state in a fashion similar to the experimentally observed HCEs. Duration of the high state is determined by the onset of feedback inhibition, which scales supralinearly with excitations. Activity was simulated for two levels (high and low) of recurrent excitation.

Poster available at: http://neurosciences.case.edu/labs/galan/publications.html