Molecular mechanisms of morphological and functional plasticity in central neurons

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Widespread efforts in trying to understand the biological basis of memory resulted in the identification of several molecular cascades involved in the formation and storage of memories in the brain, as well as the identification of the dendritic spine, the locus of synaptic interaction as the site where a 'memory' is stored. Yet, little is known about the relevance of the activation of these molecular cascades to the morphological changes in the spines, on one hand, and the functional long term neuronal plasticity, on the other. We have previously found that a brief exposure of cultured hippocampal neurons to a conditioning medium (CM) that facilitates activation of the NMDA receptor causes long-term enhancement of their synchronous spontaneous activity. This enhanced network activity was associated with an increase in the strength of excitatory connectivity among pairs of neurons, and the weakening of inhibitory connections among the neurons. It was also associated with the formation, modification and pruning of dendritic spines.

In trying to analyze the functional relevance of the changes in spine shape/size, we resorted to focal flash photolysis of caged calcium. Spine neck length was found to control the spine/dendrite communication in that flash-activated rise of free [$Ca2^{+}$]i in the spine head diffused into the parent dendrite only if the spine neck was short. Since spine neck length could vary within minutes, it serves as a dynamic filter for passage of calcium between the synapse and dendrite.

The role of dendritic morphology in cellular functions has been studied with neurons transfected with the ionotrophic excitatory glutamate receptors (GluR1-GFP). We were able to track the diffusion of these fluorescent receptors into the dendritic spines following the conditioning protocol, and following a flash activated local rise of intracellular calcium concentration. A novel molecule, synaptopodin (SP), appears to play a crucial role in this diffusion, as the reduction in the density of SP in the dendritic spine using selective siRNA, abolished the GLUR-1 response to the conditioning protocol (Fig 1, 2).

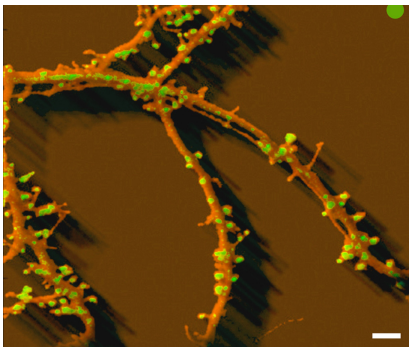

Fig. 1 *Illustration of a DsRed/GluR1-GFP co-transfected neuron, to illustrate the distribution of glutamate receptors on different types of dendritic spines in cultured cortical neuron (From Fishbein and Segal, 2007)*

Finally, the importance of spontaneous network activity was studied in cultures where activity was silenced by the use of the selective sodium channel blocker TTX. Strikingly, the lack of activity caused the slow death of the affected neurons, by activating caspase dependent processes. Small perturbations in intracellular calcium concentrations were critical in initiating the death process.

Long-term plasticity of a large network of neurons was studied in brain slices taken from rat or mice hippocampus. We examine the role of oxidative stress, evoked by raising the level of ambient H_2O_2 in the perfusion medium, on ability to express long term potentiation (LTP). Contrary to previous results and to 'common knowledge', persistent small increase in ambient H_2O_2, actually enhanced the ability to express LTP. The molecular mechanisms underlying this enhancement are beginning to be understood. Surprisingly, while the entire hippocampus is assumed to be critical for short term memories, and to express large LTP, we found that the lower fifth of this structure is unable to produce such long term changes. We are now exploring the reasons for the lack of LTP in the ventral part of the hippocampus, and associate this finding with the rather limited role of the ventral hippocampus in cognitive functions.

These results contribute to the

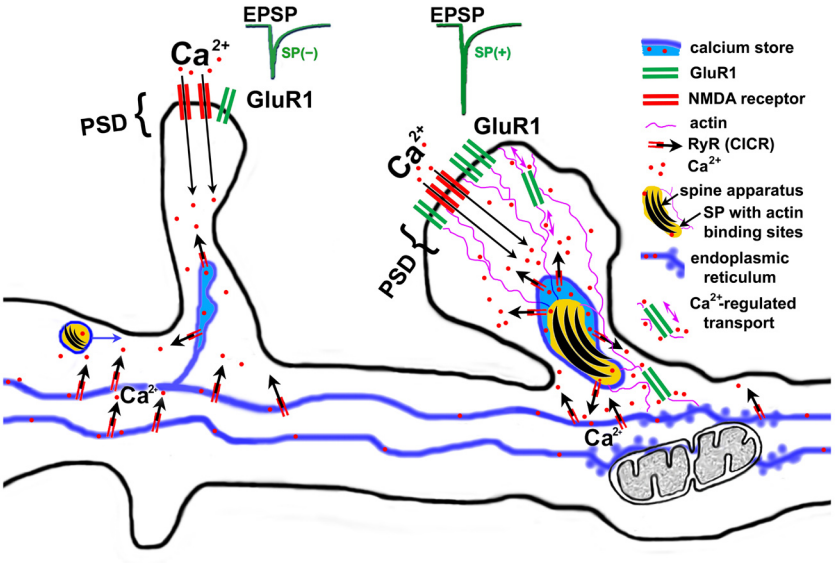

Fig. 2 *Schematic diagram of changes taking place in a dendritic spine following a 'learning ' experience. (From Korkotian et al. unpublished)*

understanding of the long term functional correlations between structure and functions of neuronal networks in the brain.

Selected publications

Segal M. (2005) Dendritic spines and long term plasticity. Nature Reviews Neurosci 6: 277-84,

Pilpel Y and Segal M. (2005) Rapid WAVE dynamics in dendritic spines of cultured hippocampal neurons is mediated by actin polymerization. J. Neurochemistry. 95:1401-1410,.

Ivenshitz M and Segal M. (2006) Simultaneous NMDA-dependent long-term potentiation of EPSCs and long-term depression of IPSCs in cultured rat hippocampal neurons. J Neurosci. 26:1199-210.

Maggio N and Segal M. (2007) Striking variations in corticosteroid modulation of long-term potentiation along the septo-temporal axis of the hippocampus J Neurosci.;27(21):5757-65.

Korkotian E and Segal M. (2007) Morphological constraints on calcium dependent glutamate receptor trafficking into individual dendritic spine.Cell Calcium. 42(1):41-57

Fishbein I and Segal M. (2007) Miniature synaptic currents become neurotoxic to chronically silenced neurons. Cerebral Cortex 17(6):1292-306

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