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Cellular Basis of Neuronal Plasticity

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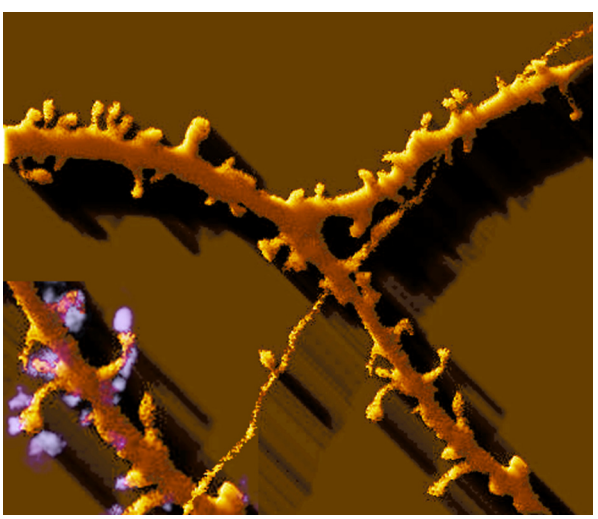
Despite widespread interest in the biological basis of memory, little is known about the relevance of morphological changes in neurons to functional neuronal plasticity. We have previously found that a brief exposure of cultured hippocampal neurons to a conditioning medium (CM) that facilitates activation of the NMDA receptor causes long-term enhancement of their spontaneous activity. Recorded on a multi-electrode array, neurons exposed to the CM expressed a long lasting increase in correlated bursting action potential discharges. This enhanced network activity was associated with protein synthesis-dependent formation, modification and pruning of dendritic spines. We examined the roles of second messenger systems, including protein kinase C the MAP-kinase ERK and CREB, in the formation of the novel dendritic spines and on network activity. A brief exposure to CM caused a rapid and specific increase in staining of neurons for both pERK and pCREB. ERK antagonist PD98059 blocked the pERK response and the formation of novel spines. A selective PKC antagonist blocked the CM-mediated formation of spines with a large head. Both the CM and PKC activation caused a delayed increase in mean amplitude of mEPSCs recorded in the hippocampal neurons, indicating a postsynaptic locus of change in synapse properties associated with the increase in network activity.

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 Rho GTPases Rho and Rac. Overexpression of these small GTPases cause marked morphological variations in neurons, with little correlated functional changes. We are now tracking the signal transduction cascade from the receptors to the effectors that are associated with regulation of cellular morphology.

Long-term plasticity of a large network of neurons is studied in brain slices taken from rat or mice hippocampus. We examine the role of oxidative stress, evoked by raising the level of ambient H2O2 in the perfusion medium, on ability to express long term potentiation (LTP). Contrary to previous results and to 'common knowledge', elevating H2O2 by a low level, actually enhances ability to express LTP. The molecular mechanisms underlying this enhancement are beginning to be understood.

One of the neurotransmitters most associated with ability to store memories is acetylcholine. In previous studies we analyzed the unique properties of acetylcholine in this respect. We now turn into the



structure in the brain that produces acetylcholine, in an attempt to understand its unique roles in the regulation of plastic properties of the higher brain structures.

Finally, we study the functional significance of spontaneous network activity in regulation of neuronal survival. Quite surprisingly, we found that blockade of spontaneous activity causes death of neurons. We are now studying the molecular mechanisms underlying this form of cell death, and the means to rescue the dying cells.

These results address the long term functional correlations between structure and functions of neuronal networks in the brain.

Selected Publications

Goldin M. Segal M and E. Avignone (2001) Functional plasticity triggers formation and pruning of dendritic spines in cultured hippocampal networks. J. Neuroscience 21: 186-193.

Segal M. Rapid plasticity of dendritic spines: hints to possible functions (2001) Prog. Neurobiol. 63: 61-70

Levkovitz Y and M. Segal (2001) Transcranial Magnetic Stimulation and antidepressive drugs share similar cellular effects in rat hippocampus. Neuropsychopharmacology.24:608-616.

Collin C., Vicario-abejon C., Rubio, M.E., Wenthold R.J. McKay R.D.G, and M. Segal (2001) Neurotrophins act at pre-synaptic terminals to activate synapses among cultured hippocampal neurons. European J. Neuroscience, 13:1273-1282

Korkotian E. and Segal M. (2001) Spike-associated fast twitches of dendritic spines in cultured hippocampal neurons. Neuron 30:751-758

Korkotian E. and Segal M (2001) Regulation of dendritic spine motility in cultured hippocampal neurons. J. Neuroscience 21: 6115-6124

Vicario-Abejon C Owens D McKay R Segal M. (2002) Role of neurotrophins in central synapse formation and stabilization. Nature Reviews Neuroscience. 3: 965-74

Segal M. (2002) Dendritic spines: elementary structural units of neuronal plasticity. Prog Brain Res.;138:53-9

Kamsler A and Segal M (2003) Hydrogen Peroxide modulation of synaptic plasticity J. Neuroscience 23:269-76

Eilam R. Peter Y. Groner Y and Segal M. (2003) Late degeneration of nigro-striatal neurons in ATM-/- mice..Neuroscience;121:83-98

Goldin M. and Segal M. (2003) Protein kinase C and ERK involvement in dendritic spine plasticity in cultured rodent hippocampal neurons Euro. J. Neurosci. 17(12):2529-39

Segal M. Greenberger V. and E. Korkotian (2003) Formation of dendritic spines in cultured striatal neurons depends on excitatory afferent activity. Euro. J. Neurosci 17(12):2573-85

Kamsler A and Segal M (2003) Paradoxical actions of hydrogen peroxide on LTP in transgenic SOD-1 mice J Neuroscience 23, 10359-67

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