BMC Neuroscience

Poster presentation

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Impaired structural plasticity increases connectivity in developing cortical networks

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from Eighteenth Annual Computational Neuroscience Meeting: CNS*2009
Berlin, Germany. 18–23 July 2009

Published: 13 July 2009

BMC Neuroscience 2009, **10**(Suppl 1):P208 doi:10.1186/1471-2202-10-S1-P208

This abstract is available from: http://www.biomedcentral.com/1471-2202/10/S1/P208

The principle of self-organization is fundamental for the adaptive formation and modification of functional circuits in many parts of the nervous system. At a cellular level, cortical micro-circuitry evolves on the basis of activity-dependent biochemical processes that guide neuronal wiring and that are differentially regulated in the course of development. Protein kinase C (PKC) plays a key-role in this morphological differentiation of neurons, since it cross-links many biochemical pathways involved in structural regulation and targets many cytoskeletal proteins directly. In a simplified model, activation of PKC via metabotropic glutamate receptor downstream signaling phosphorylates and mobilizes cytoskeletal proteins and thereby promotes structural plasticity [1]. Antagonistic pathways that involve NMDA receptor mediated activation of protein phosphatases in turn promote cytoskeletal assembly and stabilization.

We explore this concept of structural homeostasis in dissociated cortical cell cultures developing on microelectrode arrays. These generic random networks display a self-regulated maturation process with similar phases as the developing cortex. Within this period of network formation we interfered with the structural homeostasis by inhibiting PKC activity. Previous studies showed that inhibition of PKC activity in cerebellar slice cultures promotes dendritic outgrowth and arborization in Purkinje cells [2] and that climbing fiber pruning is impaired in PKC deficient mice [3]. Further in vitro data demonstrate the importance of PKC activity for the experience-dependent modulation of synaptic weights on the basis of AMPA receptor trafficking [4], suggesting reduced synaptic plasticity under PKC inhibition.

To assess possible functional consequences of these dependencies, we chronically inhibited PKC activity in cortical cell cultures and compared network activity and connectivity characteristics. Applying new morphometrics, we found significantly increased arborization and extent of dendrites as well as increased synapse density, indicating increased connectivity in these networks. Further, we observed reduced neuronal clustering suggesting impaired cell migration. These findings indicate changes in the connectivity statistics in networks developing under inhibited PKC activity that fit to the assumed homeostatic model of structural regulation. Irrespective of PKC inhibition, spike activity remained organized in network-wide bursting that characteristically emerges in cortical cell cultures. Bursts were, however, more synchronized across the recording area and contained more spikes, suggesting a faster propagation of activity through the networks and longer reverberations due to increased connectivity. Differences in the spatio-temporal spread of activity at different stages of development further indicate a more homogeneous topology under PKC inhibition. This could be the result of a stronger conservation of the highly con-

nected and unclustered immature network structure. In summary, consistence between our morphological and electrophysiological data support the idea that coordinated regulation of PKC activity is required for a proper formation of functional pathways in early network development.

Acknowledgements

Supported by the German Federal Ministry of Education and Research (FKZ 01GQ0420) and the European Community (Neuro, No. 12788).

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