SL14

Molecular control of synaptic plasticity in hippocampal neurons

Dominique Muller

Department of Neuroscience, University of Geneva, School of Medicine, 1211 Geneva 4, Switzerland

At many CNS synapses, neuronal activity triggers various forms of synaptic plasticity, involving both changes in synaptic efficacy and mechanisms of synaptic growth and remodelling of connections. These forms of plasticity are believed to be crucial for many aspects of brain development and function, including learning and memory or cognitive abilities. An important issue therefore is to understand the molecular events underlying these properties of plasticity. Work from many laboratories has provided evidence that protein kinases and particularly calcium/calmodulin dependent protein kinase II plays a major role in the control of both functional and structural plasticity. Many recent studies also demonstrated that the changes in synaptic efficacy mainly rely upon modifications of the expression of AMPA type of glutamate receptors through a complex regulation involving various postsynaptic density proteins. Much less is known however on the signalling mechanisms that participate in the processes that control synapse formation and maturation.

To this end, we recently focussed on the possible role of signalling pathways that include gene products coded by X-linked mental retardation genes. The number of genes identified as responsible for X-linked forms of mental retardation has increased exponentially over the last few years. Among these are the genes PAK3 and ARHGEF6, for which mutations have been shown to result in non-syndromic forms of mental retardation. Both PAK3 and ARHGEF6 code for proteins involved in small GTPase signalling and might therefore contribute to regulate structural aspects of synapse formation and maturation processes. To study these mechanisms, we undertook a transfection approach in organotypic hippocampal slice cultures. Several constructs were generated in order to over-express wild type PAK3 or ARHGEF6, to knockdown the proteins through antisense or siRNA approaches, or to express mutated or constitutively active forms of the molecules. We found that over-expression of wild type PAK3 or ARHGEF6 did not result in changes in the morphological characteristics of transfected cells. However, knockdown of PAK3, either through the antisense or siRNA approaches, resulted in a particular phenotype characterized by a marked decrease in the proportion of large mushroom-type spines associated with an increase in dendritic filopodia-like protrusions and elongated, thin spines. Interestingly, over-expression of PAK3 carrying the human MRX30 mutation reproduced the same phenotype as did also another mutation affecting the kinase domain of PAK3 as well as suppression of ARHGEF6. EM studies of cells expressing MRX30 mutated PAK3 revealed that many of these abnormal spines were in fact devoid of synaptic partners and did not form functional, mature synapses. Electrophysiological recordings also showed impaired plasticity at these synapses. Together these results suggest that PAK3 and ARHGEF6 are likely to be involved in the same signalling module, that this pathway contributes to spine morphogenesis and synapse maturation and that the biological mechanisms underlying the mental retardation observed with mutation of these two MRX genes are likely to be very similar.

Profile: professor of pharmacology and neuroscience, University of Geneva Medical School, Switzerland.