BMC Neuroscience

Poster presentation

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Compartimentalized NF-kappaB activity in the axon initial segment

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from Annual Meeting of the Study Group Neurochemistry. International Conference of the Gesellschaft für Biochemie und Molekularbiologie 2006 (GBM 2006): Molecular pathways in health and disease of the nervous system
Witten, Germany. 28–30 September 2006

Published: 23 March 2007

BMC Neuroscience 2007, **8**(Suppl 1):P10 doi:10.1186/1471-2202-8-S1-P10

The transcription factor NF-kappaB plays a pivotal role in the development and maintenance of the central nervous system and its constitutive activation in neurons has been previously reported. NF-kappaB is post-translationally activated upon phosphorylation of the IkappaBalpha inhibitory protein by the activated IkappaB kinase (IKKalpha/beta) and the subsequent degradation of IkappaBalpha by the proteasome. Recently, we had demonstrated an unexpected accumulation of three components of the NF-kappaB cascade in the axon initial segment (AIS): Activated IKK, phosphorylated IkappaBalpha and phosphorylated-p65(Ser536). These are all associated with detergent-insoluble cytoskeletal components of the AIS. We observed further compartimentalization as pIKKalpha/beta primarily associated with the membrane cytoskeleton, whereas pIkappaBalpha was sequestered to fasciculated microtubules. Colchicine-induced depolymerization of microtubules was associated with reduced sequestration of pIkappaBalpha in the AIS, which could be blocked by use of proteasome inhibitors like Mg-132 or Lactacystin. Concurrently, enhanced nuclear immunoreactivity for the NF-kappaB subunit p65 was noted. Using NF-kappaB-dependent reporter gene assays, a significant increase in NF-kappaB activity was observed after depolymerization of microtubules and this was inhibited by the microtubule-stabilizing drug paclitaxel. The use of transiently transfected, photoactivatable-GFP p65 fusion proteins will allow us to specifically analyse the compartimentalized signal transduction pathways in unique spatial and temporal resolution. Taken together, these observations provide strong evidence for compartmentalized activation of NF-kappaB in the AIS and modulation of neuronal NF-kappaB activity by microtubule dynamics.