BMC Neuroscience

Poster presentation

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Investigation on constitutive IKK 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):P9 doi:10.1186/1471-2202-8-S1-P9

The transcription factor NF-kappaB plays a central role in the development and maintenance of the central nervous system and its constitutive activation in neurons has been repeatedly reported. Previous work from our laboratories (poster presentation: Compartimentalized NF-kappaB activity in the axon initial segment) had revealed an intriguing clustering of activated IKKalpha/beta and other downstream elements of an activated NF-kappaB cascade (phospho-IkappaBalpha, phospho-p65(Ser536)) in the axon initial segment (AIS). Accumulation of certain voltage-gated sodium channels (Na(v)1.2), M-type potassium channels (KCNQ2) as well as cytoskeletal anchoring proteins (AnkyrinG) characterise the AIS. However, it is not yet clear how AIS-localized IKK gets activated and whether this can be connected to the constitutive activation of NF-kappaB. Long-term blockade of sodium channels with tetrodotoxin, potassium-channels with linopirdine or NMDA-receptors with MK-801 did not elicit any change upon the constitutive activation of the pathway. Strikingly, the occurrence of phosphorylated IkappaBalpha was even unaltered by 24 h of incubation with protein synthesis inhibitors. Others have reported that impairment of NF-kappaB inhibits neuritogenesis. In this line we observed that the early initiation of IkappaBalpha phosphorylation was susceptible to inhibition of IKK in DIV1–2 neurons. We therefore aim to identify the interaction partners of the activated IKK complex in the AIS. Proteomic methods such as co-immunoprecipitation analyses and mass-spectrometry will help us to identify the key players in the initiation of constitutive IKK phosphorylation and activation in neurons.