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Impact of AMPA receptors and Kir4.1 channels in grey matter NG2 glia on myelination, signal transmission and behaviour: Comparative studies in the hippocampus and cerebellum

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The physiological impact of neuron-NG2 glia synapses in grey matter is unclear. Specifically, it remains unknown under which conditions and through which mechanisms synaptically activated NG2 glia feed back to neurons. Grey matter NG2 glia display heterogeneous properties. For example, stimulus-induced postsynaptic responses of NG2 glia in the cerebellum exceed those in hippocampal NG2 cells more than 10fold. Cause and consequence of this functional diversity are not known. To investigate presumed NG2 glia-neuron back signalling and NG2 glia heterogeneity, we have generated mice with inducible NG2 cell-directed genetic deletion of AMPA receptors (quadruple GluA flox mice) and Kir4.1 channels (Kir4.1 flox mice). In the previous funding period we have found that these mice display altered myelination and synaptic plasticity. In addition we have found brain region-specific differences in the expression of auxiliary AMPA receptor subunits, which might confer higher efficiency on neuron-NG2 glia synapses in the cerebellum. In our follow-up proposal we will build on these findings and address the following questions:i) Does heterogeneous expression of AMPA receptors or auxiliary subunits contribute to the stronger responsiveness to synaptic activation of cerebellar vs. hippocampal NG2 glia?Ca2+ permeability and kinetics of GluA subunits and auxiliary subunits critically influence the efficiency of synaptic transmission. We will determine whether differences in receptor splicing and presence of the auxiliary subunit TARP gamma-2 contribute to the higher and variable responsiveness of cerebellar NG2 glia to synaptic stimulation.ii) What is the impact of AMPA receptors in hippocampal and cerebellar NG2 glia: Do synaptically activated NG2 glia signal back to neurons and influence behaviour?We will characterize on the cellular, network and behavioural level the consequences of NG2 glia-targeted deletion of AMPA receptors, to deduce their physiological impact. iii) Do Kir4.1 channels in NG2 glia influence the efficiency of their synaptic input, back signaling to neurons and behaviour?Kir4.1 flox mice display enhanced myelination and impaired neuronal plasticity. We will identify the molecular mechanism(s) underlying these alterations and investigate its behavioural consequences.

Quelle:
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