Hereditary spinal cord diseases – pathomechanistic insights using transgenic animal models

C. Neusch, Dept. of Neurology, Georg-August-University Göttingen, Germany

Hereditary spinal cord diseases, such as spastic paraplegia (SPG), leucodystrophies or familiar forms of ALS (fALS) involve degeneration of motor neurons, axons *and* glial cells. Mechanism leading to neuronal and axonal dysfunction include the loss of non-neuronal/glial proteins that are important for myelination (e. g. in SPG2) or the perineural ion and neurotransmitter homeostasis (e. g. GLT1 in fALS). In earlier studies, we investigated the impact of a major glial K_{ir} channel subunit, $K_{ir}4.1$, for spinal cord integrity by constitutive genetic inactivation. One important function of K_{ir} channels is regulating (a) the resting membrane potential of glial cells and (b) the extracellular K^+ concentration by buffering K^+ away from perineural compartments. Genetic inactivation of $K_{ir}4.1$ in mice led to early glial and secondary axonal degeneration in the spinal cord. The histopathology and the observed motor deficits with limb paresis and spasticity in these mice mimicks hereditary spinal cord diseases, e. g. leucodystrophies or SPG2. When extending our studies to a classical mouse model for fALS (G93A mutant), we found profound changes in $K_{ir}4.1$ channel expression. $K_{ir}4.1$ expression is highly reduced in affected mice from presymptomatic stages on and is almost absent in endstage fALS mice suggesting impaired K^+ buffering as pathogenic factor. Culture experiments indicated that chronic increases in K^+ levels induce motor neuron death. Axonal and neuronal degeneration in some hereditary spinal cord diseases involves the focal or genetic loss of important glial proteins, e. g. PLP, GLT1 or $K_{ir}4.1$ channels leading to disturbed neuron to glia cross-talk. The mechanistic information, we gain from these studies, help to unravel the complex multistep process terminating in motor neuron death in hereditary spinal cord diseases and may offer new therapeutic target proteins.

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