

The role of Piccolo in cerebellar circuitry

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The presynaptic active zone protein Piccolo (Pclo) is best known for its role in the formation of active zones and regulation of neurotransmitter release. Through manipulation of the PCLO gene, we have observed a specific effect of Piccolo loss-of-function (LOF) on the unique cerebellar mossy fibre (MF) synapse. We observe a profound impact on the anatomical, functional and behavioural level.

Analysis of Piccolo knockout (Pclogt/gt) brains revealed a severe reduction in brain size in comparison to wildtype (Pclowt/wt) counterparts, with reduced size of cerebellar, pontine and cortical regions. Formation of MF afferents to the cerebellum appear to be disrupted, as Pclogt/gt MF terminals are reduced to half of size of Pclowt/wt. Climbing fibre innervation of the molecular layer of Pclogt/gt cerebella is increased, indicating perturbation of the cerebellar network. We also observe a reduction in the $\alpha 6$ subunit of the GABA_A receptor, expressed at the MF, which could be a homeostatic downregulation to compensate for reduced glutamatergic input from MF boutons.

On a functional level, Pclogt/gt rats display impaired motor coordination, evidenced by failure in a rotarod task, despite adequate performance in tasks that reflect muscle strength and locomotion. We are currently undertaking electrophysiological recordings of MF boutons to further investigate the consequence of Piccolo LOF on these unique synapse structures.

A mutation in the PCLO gene has been observed in patients with Pontocerebellar hypoplasia III (PCH III), a rare developmental disorder characterised by an abnormally small cerebellum and pons, severe developmental delay, motor deficits and seizures. As the human condition shares a number of anatomical and behavioural abnormalities with the Pclogt/gt rats, we propose that the Pclogt/gt mutation can be used as a model for PCH III, providing insights into how this AZ protein contributes to the formation and function of neural circuits during development.