Differential Expression Of GABA_B Receptor Subtypes In The Cerebellum And Their Involvement In Motor Function

Charlotte Mann¹, Joshua Foster¹, Bernhard Bettler², Ian Kitchen¹, Ying Chen¹

¹Faculty of Health and Medical Sciences, University of Surrey, Guildford, GU2 7XH, United Kingdom, ²Department of Biomedicine, Institute of Physiology, Pharmazentrum, University of Basel, Basel, CH-4056, Switzerland

GABA_B receptors are the G-protein coupled receptors of the inhibitory neurotransmitter GABA. Functional GABA_B receptors require the co-assembly of the GABA_B1 and GABA_B2 subunits, and the two main isoforms of the GABA_B1 subunit, GABA_B1a and GABA_B1b, form two main receptor subtypes.

The GABA_B receptors are highly expressed in the cerebellar cortex, with the predominant expression of the GABA_B1a isoform in granule cells, and GABA_B1b in Purkinje cells. This reflects their respective roles in producing pre- and postsynaptic inhibition at the granule cell-Purkinje cell synapse. Although it is known that GABA_B receptor agonists can cause ataxia, it is not known whether the two receptor subtypes are differentially involved in cerebellar motor function and co-ordination.

The expression of GABA_B receptor subunits in the cerebellum was examined in GABA_B1a⁻/⁻ and GABA_B1b⁻/⁻ mice using immunoperoxidase labelling of the GABA_B1 and GABA_B2 subunits. We confirmed the predominant expression of GABA_B1b in Purkinje cells and GABA_B1a in granule cells, and found that the GABA_B2 immunostaining was primarily confined to the molecular layer, producing a striking array of parasagittal stripes in both wild-type and GABA_B1a⁻/⁻ mice that closely resemble the characteristic pattern of anti-zebrin II immunoreactivity. In contrast, the GABA_B1b⁻/⁻ cerebellum produced diffuse immunopositive staining throughout the molecular layer. As the GABA_B2 subunit is essential for cell surface expression of GABA_B1 and G-protein coupling, the expression pattern of GABA_B2 may represent that of functional heteromeric receptors.

To investigate whether the differential expression of GABA_B receptors in the cerebellum produces a motor deficit, a battery of behavioural tests were carried out. Footprint analysis displayed GABA_B1a⁻/⁻ mice to have wider front and hind base widths, whereas GABA_B1b⁻/⁻ mice walked with a wider hind base only. The GABA_B1a⁻/⁻ mice also showed significant deficit in the hang wire test. In addition, the GABA_B1b⁻/⁻ mice exhibited significantly increased grip strength with all four limbs in comparison to wild-type.

The presynaptic GABA_B(1a,2) receptors at the granule cell-Purkinje cell synapse may play a more prominent role than the postsynaptic GABA_B(1b,2) receptors, which are expressed in parasagittal stripes. In conclusion, the GABA_B(1a,2) and GABA_B(1b,2) receptors are differentially expressed in the cerebellum, but both subtypes are involved in motor function.