Postsynaptic $GABA_A$ receptor number and enhanced gaboxadol induced change in holding currents in Purkinje cells of the dystrophin-deficient mdx mouse

S.I. Head,[1] S.L. Kueh,[2] J. Dempster[3] and J.W. Morley,[1,2] [1]School of Medical Science, University of New South Wales, NSW 2052, Australia, [2]School of Medicine, University of Western Sydney, NSW 2560, Australia and [3]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, Scotland, UK.

Duchenne muscular dystrophy (DMD) results from an absence of the protein dystrophin. It is characterized by severe wasting of skeletal muscle. In about a third of these patients, there is evidence of an accompanying cognitive and behavioral deficit. In the cerebellum dystrophin is normally localized at the postsynaptic membrane of GABAergic synapses on Purkinje cells. Here, we investigate the effect of an absence of dystrophin on the number of $GABA_A$ channels located at the synapse in cerebellar Purkinje cells of the dystrophin-deficient mdx mouse. Whole-cell patch-clamp recordings of spontaneous miniature inhibitory postsynaptic currents (mIPSCs) were performed in cerebellar slices from mdx and littermate control mice, which had been killed by an halothane according to UNSW ethics guidelines. Using non stationary noise analysis, we found a significant difference in the number of receptors at GABAergic synapses in mdx mice (38.38 ± 2.95; n=14) compared to littermate controls (53.03 ± 4.11; n=12) (p = 0.01). In response to the application of the GABA agonist gaboxadol we found a significant difference in the gaboxadol induced change in holding current in mdx mice (65.01 ± 5.89 pA; n=9) compared to littermate controls (37.36 ± 3.82 pA; n=8). The results show that in cerebellar Purkinje cells of dystrophin-deficient mdx mice there is a reduction in the number of receptors localised at GABAergic synapses, and an increase in extrasynaptic $GABA_A$ receptors, indicating that dystrophin plays an important role in ion channel localization and stabilization at the post-synaptic membrane. If similar changes occur in the CNS in boys with DMD, it may impact on the function of neural networks and contribute to motor, behavioral and cognitive impairment apparent in many boys with DMD.