Electrophysiological and behavioural impairments in the cuprizone demyelination/remyelination mouse model

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Background – Central myelin, produced by oligodendrocytes in the central nervous system (CNS), is a lipid-rich membrane protecting and electrically isolating neuronal axons. In multiple sclerosis, myelin membranes and oligodendrocytes are destroyed through chronic inflammation in the CNS. The cuprizone murine model is a toxic model of demyelination, in which neurotoxin cuprizone is fed to mice, inducing death of oligodendrocytes and consequent CNS demyelination. If after 5 weeks of cuprizone administration, when demyelination is over 90%, mice are returned to a regular diet, spontaneous remyelination occurs, with myelination returning to 90% after 4 weeks of recovery.

Aim of the Study – To characterize electrophysiological and behavioral impairments of cuprizone-fed mice over the course of 7 weeks and subsequently, after cuprizone diet suspension, to evaluate the possible recovery of these impairments during the remyelinization phase.

Materials & Methods – Male wild-type C57BL/6 were fed cuprizone or regular diet for 7 weeks (W0-W7), after which toxin was removed and 2 weeks of recovery were allowed (RW1-2). Visual evoked potential (VEP) under ketamine/xylazine was used to evaluate optic nerve function. Epidermal VEP (Ag/AgCl cup electrode on scalp) was recorded in response to flash stimulation. Forelimb grip strength was measured through a spring dynamometer. Motor coordination was evaluated recording time to turn and time to touch down in the vertical pole test.

Results – VEP latency was significantly delayed, compared with control mice, from W4 (W4: $p = 0.0001$; W5, W6, W7: $p < 0.0001$) and was rescued at RW2. VEP amplitude was reduced at W7 ($p = 0.042$) and recovered at RW2. Grip strength was reduced at W3 ($p = 0.025$), W5 ($p = 0.002$) and W7 ($p = 0.001$), recovering at RW1. No alteration of motor coordination in pole test was observed. Body weight was significantly decreased from W1 to W7 (for all, $p < 0.01$) and was rescued at RW0.5.

Conclusions – Body weight was reduced at very early stages (since W1), followed by loss of grip strength at W3. VEP latency delay was found from W4, suggesting damage to optic nerve myelin. Reduction of VEP amplitude appeared only later at W7. Both VEP abnormalities were reverted 2 weeks after cuprizone suspension, indicating that remyelination-mediated rescue is possible. Indeed, VEP evaluation of optic nerve function in the cuprizone model could be used to test treatments aiming at boosting and/or speeding up remyelination.