Exercise attenuates myelin loss and astrogliosis in experimental Multiple Sclerosis

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Multiple Sclerosis (MS) is a chronic inflammatory neurodegenerative disease of the central nervous system (CNS), caused by an autoimmune attack against myelin antigens. Pathological hallmarks of MS brains are demyelinating lesions and a prominent astrogliosis (Compston and Coles, 2008). Rodent models of MS are the experimental autoimmune encephalomyelitis (EAE), which well recapitulates the autoimmune mechanisms of the disease, and the cuprizone (CPZ) toxicant demyelinating model, which is considered suitable to study demyelination and remyelination and to analyze the role of local inflammatory reaction, like astrogliosis (Gudi et al, 2014).

Recently, exercise training has become a well-established part of many MS rehabilitation programs. Indeed growing evidence suggests that exercise might have an impact on disease progression in both MS patients and EAE (Motl an Pilutti, 2012). However, how physical training would ultimately lead to improved quality of life in MS is still unknown.

Voluntary exercise (running wheel) in rodents best mimics exercise-based therapies in humans. Also, it is reported to promote neuroplasticity (Hannan, 2014) and to reduce clinical disability and synaptic abnormalities in EAE mice (Rossi et al, 2009). However, the impact of exercise on myelin loss, that is the pathological process linked to motor disability, is still to be clarified.

To fill this gap, we investigated the effect of voluntary exercise on demyelination and astrogliosis in the CPZ model.

8-week old C57Bl/6 female mice were randomly assigned to running wheel-equipped or standard cages the day of starting feeding with cuprizone or normal chow (experimental groups: CPZ/standard, Ctrl/standard, CPZ/exercise, Ctrl/exercise).

After 1, 3 and 5 weeks of treatment mice were evaluated for weight changes and subjected to Rotarod and grip strength tests to assess locomotor skills and neuromuscular functions. Mice were sacrificed for molecular, biochemical and histochemical studies after 6 weeks of treatment.

CPZ/standard mice showed significant weight loss and reduced latency to fall on the rotarod apparatus after 5 weeks of treatment compared to the other experimental groups (Ctrl/standard, CPZ/exercise and Ctrl/exercise). Neuromuscular function assessed by grip strength test was

already affected by CPZ and recovered by exercise after 3 weeks and the effect lasted to the fifth week.

CPZ treatment typically induces demyelination in the corpus callosum and the striatum, with minor or negligible effects on other brain areas like the cerebellum and the spinal cord, respectively (Gudi et al, 2014). We found that exercise partially prevented the myelin loss associated to CPZ treatment in the striatum/corpus callosum, without inducing per se alteration of myelin content in the same area of Ctrl/exercise mice compared to Ctrl/standard mice. We also assessed astrogliosis, which is a typical feature of the brain of CPZ-treated mice and heavily implicated in the mechanisms of damage/repair of myelin sheaths. Exercise reduced astrogliosis and inflammatory reaction in the striatum, having no effects per se in control mice.

Putative mechanisms activated by exercise are under investigation and refer to the role played by microRNAs (miRNAs) in astrocyte activation and myelin loss and to the proliferation/survival rate and/or differentiation of oligodendrocyte precursor cells (OPCs).

Overall our results indicate that exercise has beneficial effects on motor as well as pathological features, demyelination and astrogliosis, associated to CPZ treatment. Moreover, these data point to exercise as an effective adjuvant therapy to immunomodulatory drugs used in MS, due to its ability to directly activate mechanisms of myelin repair.

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