

Editorial

Inhibition of Neuroinflammation May Mediate the Disease-Modifying Effects of Exercise: Implications for Parkinson's Disease

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Accumulating evidence indicates that regularly engaging in exercise may have disease-modifying effects across neurodegenerative diseases, including Parkinson's disease (PD) [1] and Alzheimer's disease (AD) [2]. However, insights into which mechanisms mediate these effects of exercise remain limited. In last month's issue of *Nature*, De Miguel and colleagues performed several complementary experiments to investigate which mechanisms might mediate the effects of exercise on cognition in AD [3]. They found that the effects of exercise may be mediated by a reduction in neuroinflammation, due to upregulation of complement cascade inhibitors, and in particular by a complement cascade inhibiting molecule named clusterin. Their translational work could serve as a template to identify mediators of the disease-modifying effects of exercise in other neurodegenerative diseases, including PD. Here, we

briefly review the experiments done in this new study, and discuss the possible implications for research on PD, including recommendations for further work.

De Miguel and colleagues performed four experiments. First, in a transgenic AD mouse model, they collected plasma from voluntarily running mice ('runner plasma') and transfused it into sedentary mice. This transfusion reduced baseline neuroinflammatory gene expression and experimentally induced brain inflammation in the recipient animals. Second, the authors performed a proteomic analysis of the plasma of running mice. This showed an increase in the levels of anti-inflammatory factors, in particular complement cascade inhibiting molecules such as clusterin. Third, they intravenously injected clusterin in mouse models of either AD or brain inflammation. Clusterin bound with brain endothelial cells and reduced neuroinflammatory gene expression in both models. Fourth, they performed a proteomic plasma analysis in 20 men with mild cognitive impairment who participated in a 6-month exercise trial. This revealed an exercise-induced increase in plasma levels of clusterin.

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A key strength of the study was the complementary nature of the experiments. Just by itself, the finding that exercise increases peripheral levels of anti-inflammatory factors, including clusterin, did not prove that these factors mediated the effects of exercise in the brain. However, this finding was complemented by the observation that injection of clusterin actually inhibited neuroinflammation in the brain, which does suggest a causal protective role in mice. Since only 8% of findings from animal models translate into efficacy in clinical trials [4], it was still important to investigate these findings in humans. Therefore, the experiment in men with mild cognitive impairment provided a key additional insight, as it showed a similar exercise-induced increase in clusterin levels, thereby confirming the transferability of at least some of the animal model results.

The study by De Miguel and colleagues also had some limitations. Specifically, the observed rise in clusterin levels was not confirmed using independent analytical methods (such as ELISA), which raises some doubt as to whether this specific molecule was responsible for the observed inhibition in neuroinflammation. Additionally, it would have been insightful if more information had been provided on the intensity and volume of physical activities in the mouse model, what the timing and frequency of the plasma assessments was in the mouse model and trial in humans, and whether the dose of injected clusterin in mice was sufficient to yield a meaningful and sustainable effect on anti-inflammatory factor levels. Also, since the animal model was designed for AD, the authors primarily assessed the effects of exercise on the hippocampus. Although it is unlikely that the effects of exercise are limited to the hippocampus, this study did not specifically investigate the effects of exercise on regions that are prominently affected in PD, such as the substantia nigra or the striatum. Furthermore, the trial in humans only included men, which is a relevant limitation because the observed effects of clusterin in mice were more distinct in males. This notion is all the more important in light of growing evidence that points to relevant differences in disease presentation and possibly also the pathophysiology of neurodegenerative diseases between men and women [5, 6]. In addition, the trial lacked statistical power to investigate the effects of exercise on clinical or radiological endpoints, and how much of these effects were mediated by an increase in clusterin levels.

Could these provocative findings also have implications for persons with PD? We think they might.

Converging evidence from animal models [7], prospective observational studies [5, 8] and randomized controlled trials [9–11] suggests that regularly engaging in exercise may slow the pathological processes of PD. There is currently mounting interest in unravelling which mechanisms mediate the effects of exercise in PD, in order to pave the way for the development of tailored exercise treatment strategies. Within that context, the study by De Miguel and colleagues has three key implications for the PD field.

First, the study reveals a novel mechanism that may mediate the effects of exercise in PD, namely inhibition of neuroinflammation via an exercise-induced anti-inflammatory response. In fact, there are some preliminary indications that an upregulation of clusterin could indeed slow the pathological processes of PD. Specifically, *in vitro* studies show that downregulation of the expression of clusterin may enhance the aggregation of α -synuclein [12] and some, but not all [13], observational studies show that CSF levels of clusterin are elevated in people with PD [14, 15]. Also, a recent mendelian randomization study suggested that show that a genetically reduced expression of clusterin may predict early cognitive decline in PD [16]. The findings by De Miguel and colleagues should inspire future studies, such as the phase 3 *SPARX3* trial [17], to investigate whether protective effects of anti-inflammatory mechanisms in PD can be elicited by exercise. Future studies should also examine whether this putative effect interacts with other mediators of exercise benefit in PD, such as an improvement in cardiorespiratory fitness [10] and a compensatory induction of neuroplasticity [18]. Future studies in people with PD should also assess the effect of exercise on other candidate molecular mediators, such as *Klotho* [19, 20] and *irisin* [21].

Second, the use of restraint in some of the mouse models of De Miguel and colleagues highlights another putative disease-modifying mechanism of PD, namely chronic stress, which may oppose the effects of exercise. Specifically, mice were restrained and received saline injections through the tail vein, which reduced hippocampal proliferation. This is contrary to the observed effects of exercise in a separate experiment in this study. Restraint is a well-established method to evoke chronic stress in mice, which has been previously shown to increase nigrostriatal dopamine cell loss [22] and inflammation [23] in PD animal models. Taken together, the results of these separate experiments may indicate that chronic stress and exercise have opposite effects on the brain

in PD [26]. A key area for future investigations is whether the effects of exercise and chronic stress interact. If so, it could guide the design of tailored treatment regimens in PD that entail both an exercise-promoting and stress-reducing intervention. Future studies should also take note of the results of other previous mouse models, which showed that chronic unpredictable stress and chronic psychological stress may cause region-specific disruption of brain inflammatory networks [24] and social defeat [25].

Third, the experiment in humans involved men suspected of being in a prodromal phase of AD (mild cognitive impairment), which can be a template for mechanistic studies on the effects of exercise in PD. The rationale to focus on people suspected to be in a prodromal phase is that the pathological processes of AD are already present but are not yet advanced, thereby creating a larger therapeutic window for a putative disease-modifying intervention and enhancing the possibility to observe a tangible delay in disease progression. Similarly, the pathological processes of PD accumulate already during the decade-long prodromal phase of the disease. Therefore, an exciting area for future research in PD is to investigate the mechanisms through which an exercise intervention might slow the pathological processes during the prodromal phase of PD. Such studies may involve individuals who show prodromal signs of PD (e.g., a REM sleep Behaviour Disorder) as well individuals with a genetic predisposition to PD who are still asymptomatic (e.g., *LRRK2* mutation carriers). A better understanding of the effects of exercise in the earliest stages of pathology could guide strategies to prevent, or at least delay, the manifestation of overt clinical symptoms of PD.

Taken together, the seminal work by De Miguel and colleagues has set the agenda for translational studies in the field of PD, aiming to unravel the mechanisms that mediate the disease-modifying properties of exercise in PD, as a gateway to the development of tailored treatment strategies.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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