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Game-changer in the fight against Huntington's disease: Cholesterol nanoparticles restore brain function in mice

Huntington's Disease (HD) is a devastating neurodegenerative disorder characterized by progressive cognitive and motor impairment. Multiple studies have shown impaired cholesterol biosynthesis in the brains of HD patients and various rodent models and different strategies have explored to which extent modulation of brain cholesterol levels could be beneficial for HD cognitive and motor deficits. The work titled "Chronic cholesterol administration to the brain supports complete and long-lasting cognitive and motor amelioration in Huntington's disease" by Birolini et al. is the culmination of 25 years of effort by Elena Cattaneo's research group in this area.

This study builds upon previous research (Valenza et al., Embo Mol. Med. 2015) that demonstrated the reversal of cognitive deficits in R6/2 mice by increasing intracerebral cholesterol levels using first-generation cholesterol-loaded nanoparticles. However, the short lifespan of the R6/2 mouse model limited the assessment of the sustained recovery of cholesterol-raising therapies on cognitive dysfunction over time and the improvement of motor deficits. These authors' ulterior publication using a slowly-progressing zQ175DN knock-in mouse model of the disease which more closely resembles the human condition has provided the group with a more suitable model for long-term preclinical studies. Hence, in the current work, Birolini et al. tested in this mouse line the effect of the intraperitoneal injection of second-generation cholesterol-laden brain-permeable nanoparticles. The results obtained are truly impressive: the treatment gradually releases cholesterol into the brain and effectively rescues the cognitive and motor dysfunctions that characterize HD.

The authors used three treatment paradigms. In an early treatment paradigm, mice were injected twice a week during pre-symptomatic stages (5–9 weeks of age), and motor and cognitive performance was evaluated between 20 and 48 weeks of age. Declarative long-term memory and dystonic movements observed in zQ175DN mice were rescued by the cholesterol treatment up to 29 weeks of age but not at later stages. Decreased neuromuscular strength, motor skills, and associative learning observed in zQ175DN mice were not reversed by this early treatment after 45 weeks of age.

In a second experimental paradigm, mice were treated during the symptomatic phase (25–29 weeks of age). This late treatment completely restored cognitive decline assessed by novel object recognition test and neuromuscular function at 40 and 49 weeks of age. These results provide significant contributions to the field by demonstrating successful outcomes even when cholesterol treatment is initiated after the onset of the pathological symptoms.

The third strategy consisted in an "early and late" cholesterol administration strategy combined in a 2-cycle treatment. Remarkably, after this 2-cycle treatment, cognitive and motor decline observed in zQ175DN mice was reversed in most behavioral tests and at all time-points analyzed, including the later stages around 50 weeks of age. The finding that the cholesterol treatment completely counteracted cognitive defects in HD mice was further reinforced by a meta-analysis of data obtained from different studies performed to assess the impact of brain cholesterol-raising strategies on cognitive decline and Huntingtin aggregation in a total of 381 mice.

Looking for the action mechanism of the elevation of brain cholesterol, Birolini et al. found that the amelioration of motor and cognitive impairments in HD mice correlated with a reduction in mutant Huntingtin aggregates at maximum cholesterol release, suggesting that a potential role of cholesterol in clearing these toxic protein aggregates may contribute to the observed behavioral improvement. In addition, the authors show that synaptic function of striatal medium spiny neurons (MSNs) was restored by the 2-cycle cholesterol treatment in zQ175DN mice.

Cholesterol delivery to the brain appears to be a safe therapeutic option for Huntington's disease, capable of preventing or reversing cognitive and motor defects characteristic of the disease. The treatment demonstrated no significant side effects, as analyses of inflammatory status and complete necropsy performed on HD mice after the 2-cycle treatment showed no notable changes or treatment-related lesions. In addition, pharmacokinetic studies using detarium-labeled cholesterol indicated that cholesterol is completely cleared from the brain after 20 weeks post-injection. The efficacy of the treatment during the symptomatic phase is advantageous compared to strategies based on gene silencing, which have shown greater effectiveness when administered before symptom onset. This is particularly relevant in the treatment of neurodegenerative pathologies where early diagnosis in asymptomatic stages is often challenging.

This study by Birolini et al. presents robust findings supporting the use of cholesterol administration to the brain as a therapeutic strategy for HD. The chronic cholesterol treatment improved cognitive and motor impairments, reduced mutant Huntingtin aggregates, and restored synaptic function in HD mice. These results provide a strong foundation for further research and potential clinical applications of cholesterol-releasing nanoparticles as a therapy for HD patients. The next logical step is to evaluate strategies for clinical implementation, bringing this promising therapy closer to real-world application. The potential application of this treatment to other neurodegenerative pathologies characterized by the accumulation of protein aggregates and that have been linked to alterations in cerebral cholesterol metabolism, such as Alzheimer's disease and Parkinson's disease, remains open.

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