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Role of Hypercholesterolemia and Oxysterols in Neurodegeneration

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Abstract

Hypercholesterolemia and increased levels of oxysterols, the end products of cholesterol metabolism, are considered to be risk factors for neurodegeneration. In contrast to cholesterol itself, oxysterols are able to cross the blood-brain barrier and they are efficient inhibitors of cholesterol synthesis. 27-Hydroxycholesterol (27-OH) is formed by the mitochondrial cytochrome P-450 enzyme CYP27. This enzyme is present in most organs and tissues and has broad substrate specificity. Under normal conditions most of the 27-OH present in brain and in CSF originates from the circulation. Since cholesterol itself does not pass the blood-brain barrier, and there is a close relationship between cholesterol and 27-OH in the circulation, hypercholesterolemia is likely to lead to increased flux of 27-OH into the brain.

Many previous studies have suggested that high cholesterol and oxysterols levels are associated to learning and memory impairment in rodents. High cholesterol diet or 27-OH injections affect learning and memory in rodents. Moreover, animals overexpressing the enzyme CYP27A1, and in which the levels of 27-OH are 6-fold higher to wild-type, have memory impairment and reduced branches. In vitro, 27-OH-induced cytotoxicity has been demonstrated in primary hippocampal culture. High levels of oxysterols are also found in motor and demyelinating diseases however, there is not much literature on the impact of hypercholesterolemia on motor function.

In this study we report that 1µM of 27-OH induced cytotoxicity in mouse cortical primary neurons after 10 days (DIV1-10) of daily treatment.

We also found that C57Bl6 mice, at 1 year of age, fed with chow containing 1% cholesterol for 16 weeks, had reduced spine density in the motor cortex and impaired motor coordination compared to the control group, whereas there was no difference between groups in spontaneous locomotor activity or strength tests.

These data suggest that hypercholesterolemia and altered levels of oxysterols could contribute to motor-related pathologies.

Biography

Assunta Pelosi earned her PhD in Molecular Microbiology in 2010, before moving to Neurobiology. She has been working on the molecular pathways involved in hippocampal development at Medical University of Mainz, in Germany, and more recently on the molecular basis and behavioral features of motor disorders such as dystonia and L-DOPA induced dyskinesia, at INSERM in Paris. In 2018, she joined Sanofi-Aventis R&D as a postdoctoral researcher; her work focuses on the role of hypercholesterolemia in neurodegeneration.

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