Inhibition of glucocerebrosidase activity in a transgenic mice overexpressing alpha-synuclein

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Résumé

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by alpha-synuclein accumulation, neuroinflammation and loss of dopaminergic neurons and that is typically manifested by motor symptoms and nonmotor symptoms. Defects in the activity of glucocerebrosidase (GBA1), a lysosomal enzyme regulating the metabolism of glucocerebroside-based sphingolipids, is suspected to contribute to this pathogenesis. For instance loss-of-function GBA1 mutations are a major risk factors for PD and a decrease activity of GBA1 was reported in the brain of PD patients carrying or not a GBA1 mutation. The aim of our study is to better understand the impact of the inhibition of GBA1 activity on alpha-synuclein accumulation, neuroinflammation and sensorymotor functions using transgenic mice overexpressing human wild-type alpha-synuclein (Thy1-aSYN mice).

Three-month-old Thy1-aSYN and wild-type (WT) male mice were treated for 14 days by intraperitoneal injection with conduritol-beta-epoxyde (CBE; a GBA1 inhibitor; 100mg/kg/day) or PBS. Central GBA1 activity was determined by fluorogenic assay and glucocerebrosides and sphingolipids levels were quantified by mass spectrometry and thin-layer chromatography. Immune cell populations in blood and brain were numbered by multicolor flow cytometry. Peripheral and central alpha-synuclein levels are measured by ELISA and Western blot.

*Intervenant

Motor performance was evaluated in the challenging beam test and the removal adhesive test.

Our results show that CBE decreases glucocerebrosidase activity and increases glucosylceramides levels in the brain of mice. Thy1-aSyn mice treated by CBE present neurosensorial impairments in removal adhesive test an increasing number of CD45+ cells in the brain. No treatment effect is observed in the brain and the blood of transgenic or WT mice when measuring total alpha-synuclein.

Altogether, our data suggest that loss of GBA1 activity could significantly impact on neurosensorial performancesand immune response in transgenic mice overexpressing alpha-synuclein. Thus a synergistic effect between GBA1 loss of function and alpha-synuclein accumulation could contribute to such disturbances in PD. Ongoing analyses will determine the effects of GBA1 inhibition on the levels of aggregated and hyperphosphorylated forms of alpha-synuclein and on the levels of cytokines and chemokines, in order to better understand on the role of GBA1 and PD.

Mots-Clés: glucocerebrosidase, alpha, synuclein, neuroinflammation