Glucosylceramide lysosomal accumulation leads to metabolic alterations that could underlie neuronal degeneration

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β-glucocerebrosidase (GCase) is a lysosomal enzyme responsible for the catabolism of glucosylceramide (GlcCer) into glucose and ceramide. The deficiency of this enzyme causes the lysosomal accumulation of the uncatabolized GlcCer, leading to a neurodegenerative phenotype. To investigate the molecular mechanism linking GCase deficiency and the consequent GlcCer accumulation with neurodegeneration, we developed an in vitro model represented by iPSCs-derived dopaminergic neurons, obtained from a healthy subject, chronically treated with conduritol B epoxide (CBE) to inhibit GCase activity. We observed that CBE-treated neurons presented a massive lysosomal GlcCer accumulation followed by a lysosomal impairment. Considering the central role of lysosomes in the recycling of macromolecules, we investigated the effect of the lysosomal impairment on the metabolic flow through LC-MS/MS.
We observed that, following the accumulation of GlcCer, both glycolysis and the TCA cycle are affected, with a reduction in glucose content and an increase in lactate, suggesting an increased consumption of glucose due to an increased energy demand of CBE-treated neurons. We also observed in CBE-treated neurons, an overall increase in amino acid content, particularly in branched-chain amino acids, probably to fuel energy production, entering the TCA cycle, or to replenish protein synthesis, since lysosomal protein degradation and recycling are impaired.
Metabolomics analysis also revealed that acylcarnitines undergo changes with CBE treatment. In particular, the increase in short-chain acylcarnitines suggests that there may be an increased activation of β-oxidation, which would support our hypothesis of increased energy demand in CBE treated neurons.
The obtained data let to speculate that GCase loss of function impairs the lysosomal compartment, leading to severe alterations in the energetic metabolism of the neurons, switching from a glucose-centered metabolism to a protein-centered one.