Addendum III

Abstract
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Reducing GBA2 Activity Ameliorates Neuropathology in Niemann-Pick Type C Mice

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Abstract

The enzyme glucocerebrosidase (GBA) hydrolyses glucosylceramide (GlcCer) in lysosomes. Markedly reduced GBA activity is associated with severe manifestations of Gaucher disease including neurological involvement. Mutations in the GBA gene have recently also been identified as major genetic risk factor for Parkinsonism. Disturbed metabolism of GlcCer may therefore play a role in neuropathology. Besides lysosomal GBA, cells also contain a non-lysosomal glucosylceramidase (GBA2). Given that the two β-glucosidases share substrates, we speculated that over-activity of GBA2 during severe GBA impairment might influence neuropathology. This hypothesis was studied in Niemann-Pick type C (*Npc1*$^{-/-}$) mice showing secondary deficiency in GBA in various tissues. Here we report that GBA2 activity is indeed increased in the brain of *Npc1*$^{-/-}$ mice. We found that GBA2 is particularly abundant in Purkinje cells (PCs), one of the most affected neuronal populations in NPC disease. Inhibiting GBA2 in *Npc1*$^{-/-}$ mice with a brain-permeable low nanomolar inhibitor significantly improved motor coordination and extended lifespan in the absence of correction in cholesterol and ganglioside abnormalities. This trend was recapitulated, although not to full extent, by introducing a genetic loss of GBA2 in *Npc1*$^{-/-}$ mice. Our findings point to GBA2 activity as therapeutic target in NPC.

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