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LYSOSOMAL STORAGE DISEASES

Thioesterase mimetic reduces toxicity

Infantile neuronal ceroid lipofuscinosis (INCL), also known as infantile Batten disease, is a neurodegenerative lysosomal storage disease for which there is no effective treatment. In *Nature Neuroscience*, Sarkar *et al.* now report the identification of a small hydroxylamine derivative that delayed neurological deterioration and extended lifespan in a mouse model of the disease.

INCL is caused by inactivating mutations in the gene encoding palmitoyl protein thioesterase 1 (PPT1), a lysosomal enzyme that cleaves thioester linkages in palmitoylated proteins (lipid-modified proteins that are constituents of ceroid), and enables their degradation. Consequently, impaired PPT1 activity results in the accumulation of ceroid, which has devastating effects on the central nervous system (CNS).

Previous studies have shown that hydroxylamine, a nucleophilic metabolite that is found in all plants and animals, can mimic the activity of PPT1, but its haematotoxicity has prevented its therapeutic use. So, Sarkar *et al.* screened 12 hydroxylamine derivatives to identify water-soluble compounds that are able to specifically cleave thioester linkages. They selected *N*-(tert-Butyl) hydroxylamine (NtBuHA), which was deemed non-toxic and has antioxidant properties. Further experiments with lymphoblasts from patients with INCL showed that NtBuHA treatment cleaves the thioester linkage of palmitoylated proteins in a dose- and time-dependent manner. Importantly, using transmission electron microscopy, the authors showed that after 3 weeks NtBuHA drastically decreased ceroid deposition in lymphoblasts from patients with INCL.

When NtBuHA was orally administered to 3-month-old *Ppt1*$^{-/-}$ mice, which develop most of the clinical and pathological features of INCL by 6 months of age, a statistically significant decrease in ceroid deposition in the brain was observed after 3 months of treatment. The levels of oxidative and endoplasmic reticulum stress, which mediate apoptosis and are increased in INCL, were reduced in brain lysates from the NtBuHA-treated *Ppt1*$^{-/-}$ mice. A decrease in neuronal apoptosis and a delay in cortical atrophy were also observed in these mice compared with untreated *Ppt1*$^{-/-}$ mice. Interestingly, whereas the *Ppt1*-deficient mice exhibited clear signs of impaired motor coordination by 6 months, the NtBuHA-treated mice had near-normal motor coordination, confirming the delay in neurological deterioration. The lifespan of the treated mice was also extended by around 30 days.

Although the treated mice ultimately succumbed to the disease, these findings highlight the potential therapeutic benefits of small, non-toxic thioesterase mimetics with antioxidant properties for the treatment of INCL and other diseases caused by defective thioesterases and oxidative stress.

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ORIGINAL RESEARCH PAPER Sarkar, C. *et al.* Neuroprotection and lifespan extension in *Ppt1*$^{-/-}$ mice by NtBuHA: therapeutic implications for INCL. *Nature Neurosci.* http://dx.doi.org/10.1038/nn.3526 (2013)

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