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Involvement of brain pericyte damage in neuropathological changes associated with lysosomal storage

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Recent evidence suggests that peripheral blood mononuclear cells (PBMCs) contribute to the pathogenesis of neuropathological changes in patients with neuronal ceroidlipofuscinosis (NCL) and lysosomal storage diseases. In order to examine the possible increase in the permeability of the blood-brain-barrier (BBB) and resultant infiltration of PBMCs due to cathepsin D (CatD) deficiency, a process underlying the onset of congenital NCL, we examined structural changes in brain vessels in CatD-/- mice. Consequently, the mean diameter of the brain vessels in the cerebral cortex on postnatal day 24 (P24) was significantly larger in CatD-/- mice than in wild type mice. Furthermore, the mean number of brain pericytesin CatD-/- mice began to decline significantly on P16 and almost disappeared by P24, and oxidative DNA damage was first detected in brain pericytes on P12. Examinations with electron microscopy revealed that brain pericytes were laden with dense granular bodies, cytoplasmic vacuoles and lipid droplets. Moreover, pepstatin A, a specific aspartic protease inhibitor, induced mitochondria derived reactive oxygen species (ROS)production in the isolated brain pericytes, which decreased the cell viability. These observations suggest that increased lysosomal storage due to CatD deficiency causes oxidative damage in brain pericytes, subsequently resulting in an increased vessel diameter, enhanced permeability of the BBB and the infiltration of PBMCs.

Recently, much attention has been paid topericytesas a novel therapeutic target for modifing disease progression in patients with neurodegenerative disorders, such as Alzheimer's disease. In cases of diabetic retinopathy, erythropoietin may alsobe used as a novel therapeutic agent preventing the drop-out of pericytesfrom the retinal capillaries. Therefore, the use of agents capable of protecting brain pericytes against oxidative damage may provide the basis for developing alternative therapies for the treatment of neurodegenerative disorders, including NCL and Alzheimer's disease.

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