



PRINCIPE FELIPE
CENTRO DE INVESTIGACION

THE FUTURE OF BIOMEDICAL RESEARCH CIPF Lecture Series

BrainCure: Therapy for Neurodegeneration with Brain Iron Accumulation

Speaker: **José A. Sánchez Alcázar**
Universidad Pablo de Olavide-CSIC
Date: **14/12/18- 12:30h**
Place: Salón de Actos CIPF

Abstract: Neurodegeneration with brain iron accumulation (NBIA) is a group of inherited neurologic disorders in which iron accumulates in the basal ganglia resulting in progressive dystonia, spasticity, parkinsonism, neuropsychiatric abnormalities, and optic atrophy or retinal degeneration. The most prevalent form of NBIA is pantothenate kinase-associated neurodegeneration (PKAN) associated with mutations in the gene of pantothenate kinase 2 (PANK2), which is essential for coenzyme A (CoA) synthesis. There is no cure for NBIA nor is there a standard course of treatment. In our work, we have demonstrated that fibroblasts derived from patients harbouring PANK2 mutations can reproduce many of the cellular pathological alterations found in the disease, such as intracellular iron and lipofuscin accumulation, increased oxidative stress, and mitochondrial dysfunction. Furthermore, mutant fibroblasts showed a characteristic senescent morphology. Treatment with pantothenate, the PANK2 enzyme substrate, was able to correct all pathological alterations in responder mutant fibroblasts with residual PANK2 enzyme expression. However, pantothenate had no effect on mutant fibroblasts with truncated/incomplete protein expression. The positive effect of pantothenate in particular mutations was also confirmed in induced neurons obtained by direct reprogramming of mutant fibroblasts. Our results suggest that pantothenate treatment can stabilize the expression levels of PANK2 in selected mutations. These results encourage us to propose our screening model as a quick and easy way to detect pantothenate-responder patients with PANK2 mutations. The existence of residual enzyme expression in some affected individuals raises the possibility of treatment using high dose of pantothenate.

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