Niemann-Pick type C (NPC) disease is caused by a mutation of NPC1 gene on chromosome 18. NPC1 mutation leads to accumulate cholesterol in the lysosomal and late endosomal compartment and the progressive neurodegeneration of central nerve system, which leads to premature death. NPC disease may appear as early as a few months old or as late as adulthood and lead to die before 15 years old without replacement of new neuronal cells. Currently, there is no effective therapy for NPC patients. Therefore, stem cells-based therapy may be promising treatment for NPC diseases. The objective of this study was to investigate molecular mechanisms of self renewal and differentiation of neural stem cells (NSCs) using NPC1 gene knock out mice model in vitro and in vivo.

NPC1 gene deficient mice (NPC1/-) showed impaired self renewal ability and differentiation of NSCs. It was examined whether nitric oxide (NO) mediates the self-renewal ability of neural stem cells in NPC1/- mice. It was found that NO production was significantly increased in NSCs of NPC1/- mice resulting in low self-renewal ability. Activation of glycogen synthesis kinase-3beta (GSK3beta) and Caspase-3 by NO was also observed in NSCs of NPC1/- mice. NSCs selfrenewal ability was restored after inhibition of GSK3beta and Caspase-3 by the NO inhibitor (L-NAME). It is concluded that the over production of NO in NPC diseases might mainly involve in the impaired self renewal and differentiation of neural stem cells. Therefore, it is suggested that controlling of NO production might be a key factor for treatment of NPC diseases.

Molecular mechanisms regulating gene transcription resulting in NSCs differentiation in NPC disease is unknown. It was examined whether valproic acid (VPA), a histone deacetylase (HDAC) inhibitor, could enhance neuronal differentiation and recover defective cholesterol metabolism in NSCs from NPC1/- mice. VPA could induce neuronal differentiation and restore impaired astrocytes in NSCs from NPC1/- mice. Importantly, an increasing level of cholesterol within NSCs from NPC1/- mice could be reduced by VPA. Moreover, essential neurotrophic genes (TrkB, BDNF, MnSoD, and NeuroD) were up-regulated through the repression of the repressor element-1 binding site (RE1)-silencing transcription factor (REST/NRSF) and HDAC complex by the VPA treatment. Up-regulated neurotrophic genes were able to enhance neural differentiation and cholesterol homeostasis in neural stem cells from NPC1/- mice. This study suggested that, along with cholesterol homeostasis, impaired neuronal differentiation and abnormal morphology of astrocytes could be rescued by the inhibition of HDAC and REST/NRSF activity induced by VPA treatment.

It was also observed that stem cells population were decreased and abnormal morphology of neurons were found in NPC1/-mice brain in vivo (8weeks). Wnt and two receptor genes were dramatically reduced in brain of the NPC1/-mice (Wnt1, Wnt3, Wnt 7a, Fzd 3, Fzd 5, Fzd 9 and LRP5). The inactivation of Wnt signaling could contribute to lack of the self renewal and differentiation in NSCs as well as accelerate neurodegeneration in NPC disease. This study suggested that NO mediated signaling impaired self renewal and differentiations in NSCs in NPC1/- mice. HDAC inhibitor, VPA has shown effect to promote neural differentiation and recover defective cholesterol metabolism in NSCs in NPC1/- mice through the histone acetylation. Inactivation of Wnt singling may involve in features of neurological and stem cells in NPC diseases. These results will provide new insight into understating of basic mechanism for application of the stem cells therapy in NPC disease.

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