Neuroprotective effects of DNIC-1 in a transgenic mouse model of amyotrophic lateral sclerosis

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Neuroprotection seeks to preserve neural structures and functions to prevent or delay nervous system deterioration caused by aging, disease, or trauma. Previous research demonstrated the neuroprotective effects of DNIC-1 (dinitrosyl iron complex-1), a novel and stable nitric oxide (NO)-releasing compound, in a western diet-induced cognitive decline mouse model and in Drosophila models of poly-Q disease. DNIC-1 treatment alleviated neurodegeneration symptoms such as cognitive decline, increased neuronal cell death, abnormal protein aggregation, and impaired motor function. However, its potential neuroprotective effects in other neurodegenerative diseases remain unexplored. Amyotrophic lateral sclerosis (ALS) is one of the fatal neurodegenerative disorders characterized by progressive loss of motor neurons, with unclear etiology and pathophysiology, and currently lacks an effective cure. This study aimed to evaluate the neuroprotective effects of DNIC-1 in ALS animal models.

In humans, mutations in the Cu, Zn superoxide dismutase gene (SOD1) are present in 20% of familial ALS cases. Transgenic mice expressing a human SOD1 mutation (Gly-93 to Ala; G93A) develop an ALS-like motor neuron disease, making them a widely used ALS model. In this study, DNIC-1 was administered via drinking water at doses of 2.65 mg/kg/day from weeks 10 to 20, and 5.3 mg/kg/day from weeks 15 to 20. Control groups received no DNIC-1. ALS onset was monitored weekly from weeks 6 to 20 through behavioral assessments, including wire hanging and hind-limb extension tests. At study end, animals were euthanized with urethane overdose (2.0 g/kg, i.p.), and spinal cords were collected for immunohistochemical (IHC) staining and RNA sequencing (RNA-seq) analyses.

Results indicated that low-dose DNIC-1 treatment modestly delayed motor function decline in early-stage ALS mice, whereas a higher dose substantially delayed motor deterioration in middle-stage ALS mice. IHC analyses revealed that low-dose treatment significantly increased motor neuron survival, reduced astrocyte activation, and slightly decreased abnormal SOD1 aggregation in the spinal cord. RNA-seq identified 165 genes altered by the SOD1-G93A mutation; low-dose DNIC-1 minimally affected gene expression in control mice but altered 223 genes in ALS mice. Overall, optimal DNIC-1 dosing significantly delayed ALS progression, suggesting promising neuroprotective effects. Further research is warranted to clarify the mechanisms underlying DNIC-1’s neuroprotection and to refine its therapeutic application. These findings provide new perspectives on ALS pathophysiology and potential treatment strategies