Brain Permeable Iron Chelators VK-28 and M30 Rescue Degenerated Nigral Dopamine Neurons in Animal Model of PD

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RESULTS

A pivotal role of iron in the pathogenesis of PD has been hypothesized since numerous studies have shown a progressive accumulation of iron and ferritin in PD patients, specifically in the SN pars compacta (1, 2). The major mechanism of iron-mediated damage in nigrostriatal neurons is related to the fact that iron is a significant generator of reactive oxygen species (ROS) (3). Recent research has shown that iron chelation has been proven to protect neurodegeneration in PD animal model induced by N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP). Chelation of iron, either by the oral administration of iron chelators or over-expression of the heavy subunit of the iron-binding protein ferritin, protected DA neurons, maintained DA production, and prevented the motor deficits associated with MPTP administration (4). More recently, iron has been found in the rim of Lewy body where α-synuclein, ubiquitin, and tyrosine hydroxylase (TH) are also present (5). Furthermore, there is also evidence that iron overload facilitates the fibrillation of human α-synuclein and impairs the proteasomal activity (6, 7).

In the present study, we further evaluated the neurorescue properties of two newly developed brain permeable iron chelators VK-28 [5-(4-(2-hydroxyethyl)piperazin-1-yl (methyl)-8-hydroxyquinoline] and M30 [5-(N-methyl-N-propargylaminomethyl)-8-hydroxyquinoline] in vivo, against nigrostriatal degeneration induced by lactacystin.

METHODS

60 C57BL/6 mice were bilateral injected with lactacystin (1.25ug/mouse) into medial forebrain bundle (MFB) using the following coordinates (in mm): (1.34 posterior, ±1.17 lateral, and 5.1 ventral from bregma). Continuous intraperitoneal administration of VK-28 (5mg/kg/day) or M30 (5mg/kg/day) was introduce 7 days after the microinjection. The animals were sacrificed 28 days after the microinjection with lactacystin. Locomotive activity and rotarod tests were performed weekly to evaluate the behavioral changes. Neurodegeneration and nigrostriatal deficiency induced by lactacystin were indicated by immunostaining of TH-positive cells and HPLC assay of DA and its metabolites. Proteasome activity assay was applied to determine the proteasomal dysfunction produced by lactacystin. Tissue iron concentrations in midbrain were determined spectrophotometrically to manifest the change of iron after lactacystin lesion. Immunostaining of CD11b-positive cells and GFAP-positive cells was introduced to indicate the microglial activation after microinjection of lactacystin.

CONCLUSIONS

•Both VK-28 and M30 have showed marked rescuing effects on DA neurons against neurodegeneration induced by ubiquitin-proteasome system (UPS) failure.
•Bifunctional drug M30 seems to be more potent than VK-28 in the UPS-impairment induced animal model of PD.
•The result of this study may warrant further preclinical and clinical tests both VK-28 and M30 potentials in the treatment of PD.

REFERENCES