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New 8-hydroxyquinoline derivatives as promising therapeutic approaches targeting neurodegeneration

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Abstract

Background: Alzheimer's disease, Parkinson's disease, and Amyotrophic lateral sclerosis are recognized as the most prevalent neurodegenerative diseases (NDs), presenting a huge burden for society. These diseases share common pathophysiological mechanisms, such oxidative stress, dysfunction in iron metabolism, ferroptosis, and protein misfolding [1-4]. Given their powerful metal chelating and antioxidant properties, 8-hydroxyquinoline (8-HQs) derivatives have emerged as attractive therapeutic approaches for the development of innovative therapies for NDs [5]. **Objective:** To assess, *in vitro*, the neuroprotective effects of 12 newly synthesized 8-HQs with iron chelation and radical scavenging capacity, using differentiated neuronal SH-SY5Y cells as an *in vitro* model. **Methods:** The cytotoxicity of 8-HQs was initially evaluated using the MTT reduction and neutral red uptake assays, 24 hours after exposure, to select non-cytotoxic concentrations. The neuroprotective effects of the 8-HQs against the cytotoxicity induced by iron (III), erastin (a ferroptosis inducer), or by the combination of the two aggressors, were then evaluated. Their capacity to decrease *tert*-butyl hydroperoxide (*t*-BHP)-induced cytotoxicity was also investigated, aiming to elucidate the potential of the novel 8-HQs derivatives to counteract oxidative stress. The most promising 8-HQs were also tested for their ability to protect against the neurotoxin 1-methyl-4-phenylpyridinium (MPP^+), which is frequently used to mimic Parkinson's disease in *in vitro* models [6]. **Results:** Some of the 8-HQs significantly protected SH-SY5Y cells against the cytotoxicity induced by iron (III), erastin, or by the combined effects iron (III) + erastin. Moreover, several 8-HQs also remarkably reduced the cytotoxic effects induced by both *t*-BHP and MPP^+. **Conclusions:** The 8-HQs showed outstanding neuroprotective properties against the harmful effects induced by distinct chemical aggressors, highlighting their potential to become effective disease-modifying agents for counteracting neurodegeneration.

Keywords: neurodegenerative diseases; 8-hydroxyquinolines; SH-SY5Y cells; oxidative stress; ferroptosis

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