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Research Report

Stabilization of HIF-1α by FG-4592 promotes functional recovery and neural protection in experimental spinal cord injury

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ABSTRACT

Previous studies have shown that inhibition of prolyl hydroxylase(PHD) stabilizes Hypoxia-inducible factor 1, alpha subunit(HIF-1α), increases tolerance to hypoxia, and improves the prognosis of many diseases. However, the role of PHD inhibitor (PHDI) in the recovery of spinal cord injury remains controversial. In this study, we investigated the protective role of a novel PHDI FG-4592 both in vivo and in vitro. FG-4592 treatment stabilized HIF1α expression both in PC12 cells and in spinal cord. FG-4592 treatment significantly inhibited tert-Butyl hydroperoxide(TBHP)-induced apoptosis and increases the survival of neuronal PC-12 cells. FG-4592 administration also improved recovery and increased the survival of neurons in spinal cord lesions in the mice model. Combination therapy including the specific HIF-1α blocker YC-1 down-regulated the HIF-1α expression and partially abolished the protective effect of FG-4592. Taken together, our results revealed that the role of FG-4592 in SCI recovery is related to the stabilization of HIF-1α and inhibition of apoptosis. Overall, our study suggests that PHDIs may be feasible candidates for therapeutic intervention after SCI and central nervous system disorders in humans.

1. Introduction

Traumatic spinal cord injury (SCI) is one of the most severe devastating diseases, which leads to neurological deficits and motor and sensory dysfunctions. In the United States alone, it is estimated that the number of people who are living with SCI is approximately 273,000 persons in 2013, and the annual incidence of SCI is approximately 40 cases per million population (National Spinal Cord Injury Statistical Center, 2014). In Asian countries, the reported incidence rates ranged

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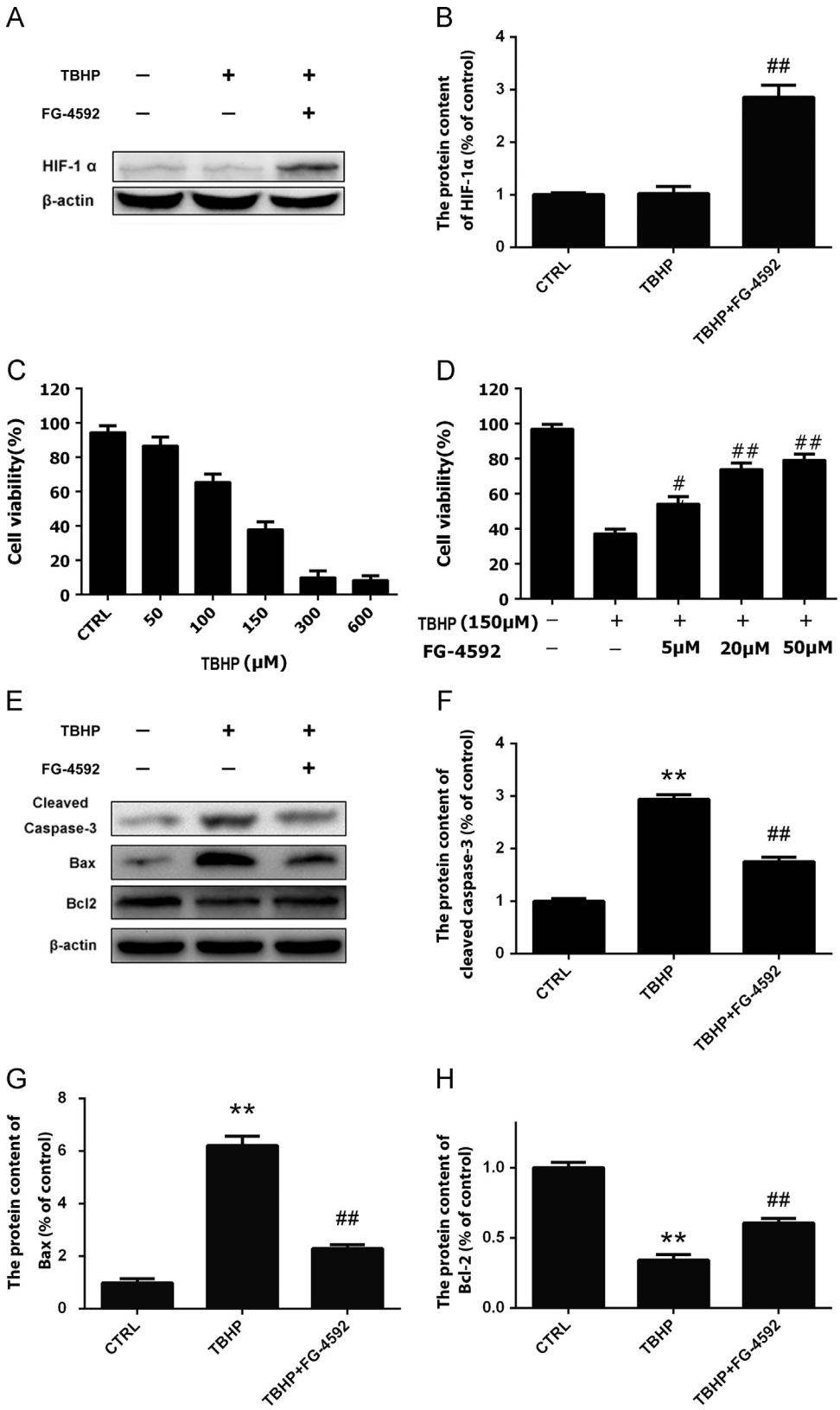

Fig. 1 – FG-4592 treatment stabilizes HIF-1α and inhibits TBHP-induced PC12 cell apoptosis. (A–B) Protein content of Hypoxia-inducible factor 1, alpha subunit (HIF-1α) of PC12 cells treated with tert-Butyl hydroperoxide (TBHP) and TBHP plus FG-4592. (C) Cell Counting Kit-8 (CCK-8) results of PC12 cells treated with different concentrations of TBHP. (D) CCK-8 results of FG-4592 treated PC12 cells induced by TBHP. (E–H) Protein content of cleaved caspase 3, Bcl-2 and Bax of PC12 cells treated with TBHP and TBHP plus FG-4592. $^{**}P<0.01$ versus the CTRL group, $\#\#P<0.01$ versus the TBHP group.