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Research Report

Deferoxamine alleviates chronic hydrocephalus after intraventricular hemorrhage through iron chelation and Wnt1/Wnt3a inhibition

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ABSTRACT

Post-hemorrhagic chronic hydrocephalus (PHCH) is a common complication after intraventricular hemorrhage (IVH). The mechanism of PHCH is not fully understood, and its treatment is relatively difficult. In the present study, a rat model of PHCH was used to elucidate the role of iron in the pathogenesis of PHCH. The action of deferoxamine (DFX) in IVH-induced PHCH, the expression of brain ferritin, the concentration of iron in cerebrospinal fluid (CSF), and changes in Wnt1/Wnt3a gene expression were determined. Results indicate that iron plays an important role in the occurrence of hydrocephalus after IVH. The iron chelator, DFX, can decrease the concentrations of iron and ferritin after cerebral hemorrhage and can thereby decrease the incidence of hydrocephalus. In addition, after IVH, the gene expression of Wnt1 and Wnt3a was enhanced, with protein expression also upregulated; DFX was able to suppress both gene and protein expression of Wnt1 and Wnt3a in brain tissue. This indicates that iron may be the key stimulus that activates the Wnt signaling pathway and regulates subarachnoid fibrosis after cerebral hemorrhage, and that DFX may be a candidate for preventing PHCH in patients with IVH.

1. Introduction

Post-hemorrhagic chronic hydrocephalus (PHCH) is a common complication subsequent to intraventricular hemorrhage (IVH) (Whitelaw, 2001). The occurrence of hydrocephalus is a key factor predicting a poor prognosis, including damage to brain parenchyma, a prominent cause of disability, that if sufficiently serious, may also lead to patient mortality (Phan et al., 2000; Hanley, 2009; Diringer et al., 1998; Bhattathiri et al., 2006; Hwang et al., 2012). Several recent studies have suggested that ferric ions generated by the catabolism of red blood cell hemoglobin subsequent to cerebral hemorrhage can somehow provoke damage to periventricular white matter (Xi et al., 2006; Wu et al., 2003). In addition to an increase in CSF iron concentration, the ferritin content in brain parenchyma has also been observed to increase in hydrocephalus patients after IVH (Chen et al., 2011). Given ferritin's role in iron storage, this finding suggests an appropriate adaptive cellular response to

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increased CSF iron concentration, and therefore, constitutes an indirect indicator of iron overload, further suggesting that iron may play some important role in PHCH (Chen et al., 2011).

In addition, it has been observed that subarachnoid fibrosis after cerebral hemorrhage appears to be a potentially important change associated with the pathogenesis of PHCH (Massicotte and Del Bigio, 1999; Mayfrank et al., 1997). Other recent studies have indicated an intimate involvement between the Wnt signaling pathway and the occurrence of fibrotic lesions in a variety of tissues, including, pulmonary, renal, and hepatic fibrosis, as well as other instances of fibroid formation (Cisternas et al., 2014; Miao et al., 2013). Given the finding of subarachnoid fibrosis in chronic hydrocephalus, this points to a potential connection between Wnt signaling and the pathogenesis of chronic hydrocephalus after IVH.

Deferoxamine (DFX), an iron chelator, has been shown to be neuroprotective in rat and pig models of intracerebral hemorrhage (ICH) and this finding has prompted a phase-I clinical trial of DFX in ICH patients (Gu et al., 2009; Okauchi et al., 2010; Selim, 2009), despite the fact that the neuroprotective mechanisms of action of DFX in IVH-induced CH is still unclear. In this report, it is hypothesized that DFX may alleviate PHCH through chelating iron and thereby inhibiting Wnt1/Wnt3a activation. In order to test this hypothesis, a rat model of PHCH was used to determine the mechanism of DFX action in IVH-induced CH, specifically with respect to increased amounts of ferritin in brain parenchyma, increased CSF iron concentration, and changes in the expression of Wnt1/Wnt3a.

2. Results

2.1. DFX alleviates the occurrence of PHCH

No occurrence of hydrocephalus was observed in the saline controls. Blood injection (IVH group) induced hydrocephalus in 8 of 10 rats (80%) at 7 and 28 days. $FeCl_3$ injection ($FeCl_3$ group) induced hydrocephalus in 6 of 10 rats (60%) at 7 days and in 7 of 10 rats at 28 days (70%). DFX was able to

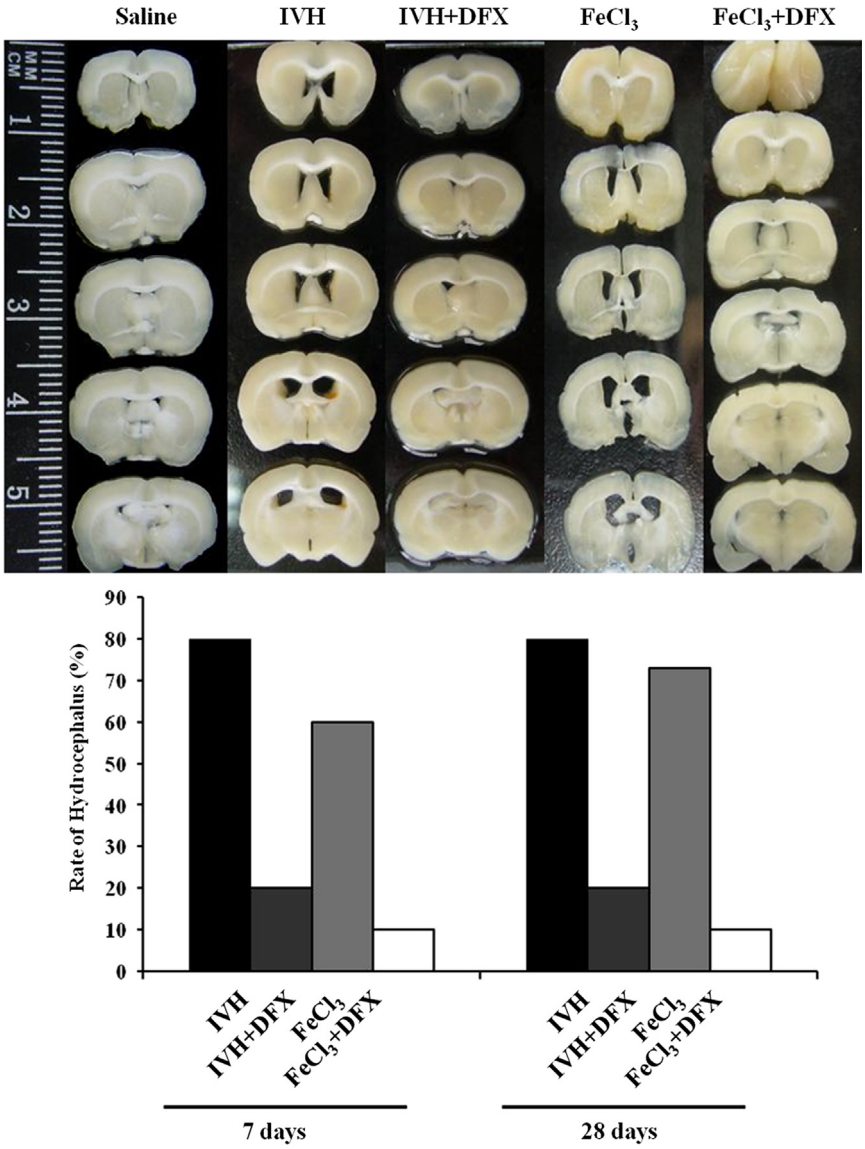

Fig. 1 – Occurrence of PHCH. (A) Slices of rat brain at day 28 after injections. (B) Rate of PHCH ($n=10$).