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Research article

Impaired adult hippocampal neurogenesis and cognitive ability in a mouse model of intrastriatal hemorrhage

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HIGHLIGHTS

- Neurogenesis was damaged in thrombin induced ICH.
- The impaired adult neurogenesis correlated with cognitive deficits.
- Apoptosis at SVZ and SGZ is not related to ICH-induced neurogenesis reduction.

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ABSTRACT

Thrombin released by hematoma is an important mediator of the secondary injury of intracerebral hemorrhage (ICH), however, the effect of thrombin on adult neurogenesis and cognitive ability remains elusive. In this study, intrastriatal injection of 0.05 U thrombin did not affect the neurogenesis at the subgranular zone (SGZ), which was distal to the injection site. 0.1 U thrombin increased the 5-bromo-2-deoxyuridine$^+$ (BrdU$^+$, S-phase proliferating cells)/doublecortin$^+$ (DCX$^+$, immature neurons) double labelled neurons, but decreased BrdU$^+$/NeuN$^+$ double labelled mature neurons. Higher doses of thrombin (1 U, 2 U, and 5 U) significantly decreased the BrdU$^+$/DCX$^+$ and BrdU$^+$/NeuN$^+$ double labelled cells. After 1 U thrombin injection, cell apoptosis was found at the dentate gyrus of hippocampus at 3–24 h, but not 5 d post-injury. Thrombin infusion (1U) induced spatial memory deficits in Morris water maze test; whereas, hirudin, the thrombin antagonist, significantly reversed both neurogenesis loss and spatial learning and memory impairment. In conclusion, at least at short term (5 days) after striatum ICH, the effect of high dose of thrombin on neurogenesis of SGZ, and the spatial learning and memory ability, is detrimental.

1. Introduction

Cognitive impairment has been reported in up to 50% survivors of intracerebral hemorrhage (ICH), which is related to poor life quality [1]. To date, no effective therapeutic achievements have been developed for the treatment of cognitive impairment [2]. Cognitive ability, usually represented by spatial learning and memory in mice, is related to the neurogenesis at subgranular zone (SGZ) of hippocampus [3]. The decline of the adult neurogenesis is correlated with a significant reduction in Morris water maze performance [4].

ICH induced brain injury is composed of primary and secondary mechanisms [5]. The primary mechanism, such as space-occupying effect of hematomas, does not constitute the whole injury [2]. The secondary injuries, which are mainly mediated by the enzymes or cytokines released by hematoma, are largely responsible for the injuries in ICH, and can't be stopped or reversed by current available medications.

Much evidence shows that thrombin is one of the main detrimental molecules in ICH-induced secondary injury [5]. Thrombin injection into the brain tissues causes lysis of vascular basement membrane, injury of neurons and astrocytes, disruption of BBB [6], and brain edema [5] in animal models. Hirudin can inhibit thrombin activity after ICH and effectively reduce the damage mentioned above [6,7].

The striatum is the most common site of ICH in patients. Striatum injury has also been produced and examined in animal ICH

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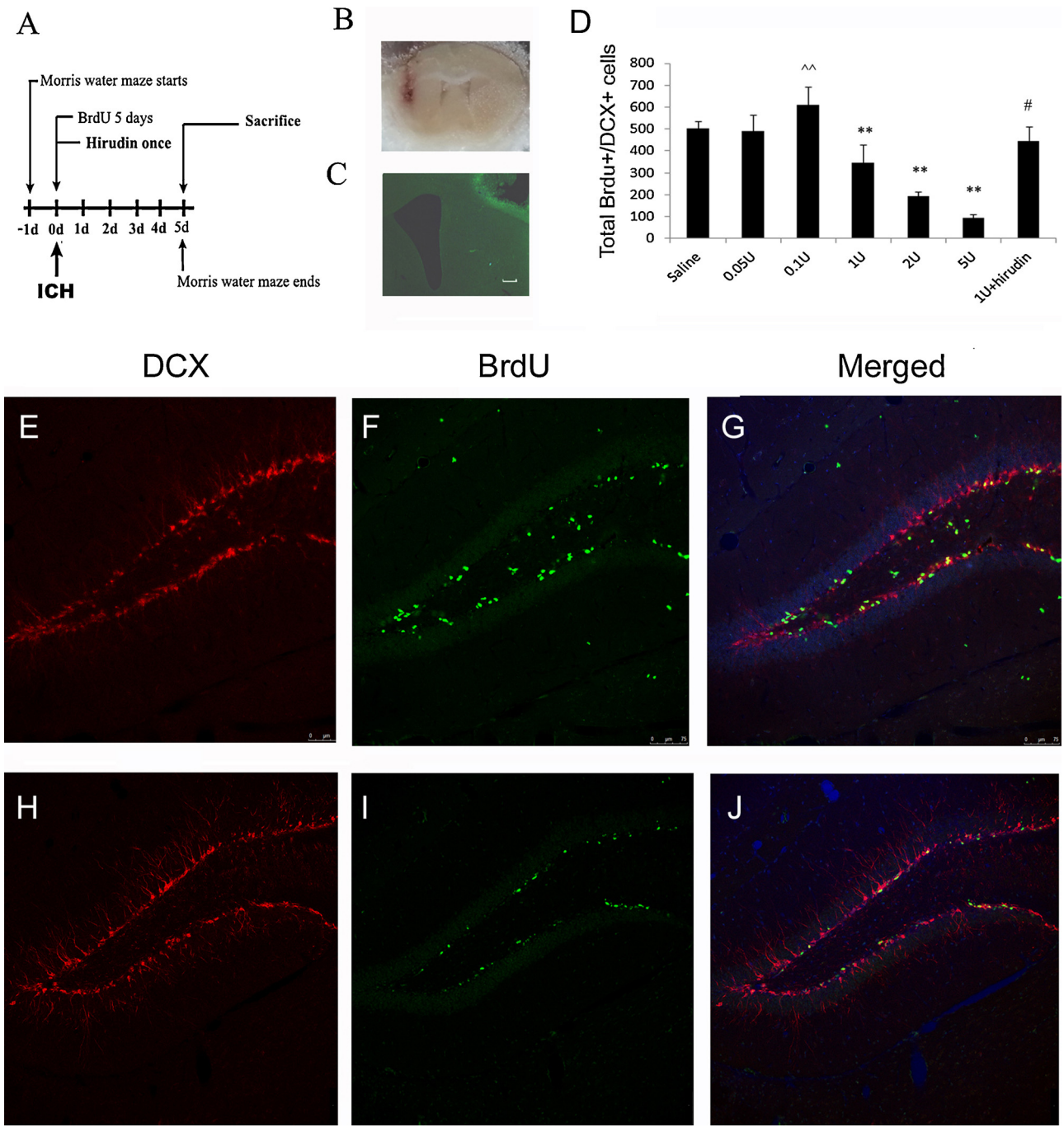

Fig. 1. High doses of thrombin decreased BrdU$^+$/DCX$^+$ immature neuron in SGZ.
(A) The experimental paradigm. Only the 1 U thrombin treatment group was selected for cognitive assessment. (B) The injection tract and hematoma produced by 5 U thrombin could be recognized by the presence of blood, tissue fraction, or necrosis. (C) The right lateral ventricle was located in the vicinity of the thrombin infusion site, whereas SGZ was distal to the injection tract and could not be seen on the graph. (D) 0.05 U thrombin did not change BrdU$^+$/DCX$^+$ cell number. 0.1 U significantly increased ($^{\wedge\wedge}p < 0.01$, compared with sham), while 1 U, 2 U and 5 U thrombin significantly decreased the BrdU$^+$/DCX$^+$ cells in SGZ of ipsilateral dentate gyrus ($^*p < 0.05$, $^{**}p < 0.01$, compared with sham). The number of BrdU$^+$/DCX$^+$ cells was dramatically reversed by hirudin treatment. ($\#p < 0.05$, compared with 1 U group). (E–G) The representative BrdU$^+$/DCX$^+$ images of Sham group. (H–J) The representative BrdU$^+$/DCX$^+$ images of 1 U thrombin group. (E, H): DCX, (F, I): BrdU, (G, J): merged images of BrdU$^+$ and DCX$^+$. Red: DCX, Green: BrdU, $n = 8$; E–J, Scale bar = 75 μm, C, Scale bar = 50 μm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

models [8]. However, the range of injury induced by intrastriatal thrombin injection is still unclear. SGZ is the region in the adult brain that maintains the neurogenesis ability throughout life [9]. The effects of intrastriatal thrombin injection on the adult neurogenesis in the SGZ and therefor the cognitive ability are still unknown.

One in vivo study demonstrates that intrastriatal thrombin injection can activate microglial cells in the midbrain and cause dopaminergic neuronal death [10]. Along the rostral to caudal axis of the brain, the substantial nigra is located further away from the thrombin injection site than hippocampus. So we can only speculate that intrastriatal thrombin injection may have impact on the adult neurogenesis at the SGZ.

In this study, we investigated the effect of striatal thrombin injection on the adult neurogenesis at SGZ, as well as hippocampal dependent learning and memory. We found that thrombin injection posed dose-dependent effects on the adult neurogenesis at the