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Research Report

Treadmill running improves motor function and alters dendritic morphology in the striatum after collagenase-induced intracerebral hemorrhage in rats

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ABSTRACT

It is well known that early rehabilitation is effective for functional recovery after intracerebral hemorrhage (ICH); however, the mechanisms have not been well described. The purpose of this study was to elucidate the effects of early rehabilitative therapy (treadmill running) on recovery of motor function and alteration of brain histology after ICH. Male Wistar rats, under deep anesthesia, were placed in a stereotaxic apparatus and injected with collagenase into the left striatum to induce ICH. Sham operated animals were treated with saline. All animals were randomly assigned to treadmill exercise (for 30 min/day, 9 m/min, between 4 and 14 days after surgery) and control and were designated to one of four groups: sham+control (SC), sham+treadmill (ST), ICH+control (IC), ICH+treadmill (IT). Motor deficit score (MDS) was assessed daily after surgery. Volume of tissue lost, dendritic morphology and PSD-95 protein level in the striatum were analyzed at 15 days after surgery. The MDS of IT was significantly improved compared with IC over time. There were no differences between IT and IC in the volume of tissue lost (IT: 63.8%, IC: 61.8%), spine density or PSD-95 protein level in the striatum. However, dendritic length was increased and arborization was more complex in the contralateral striatum of the IT than the IC group (IT: 1226 μm, IC: 937 μm). These data suggest that treadmill running improves motor function after ICH and that improvement may be related to alteration of dendritic morphology in the striatum.

1. Introduction

Intracerebral hemorrhage (ICH) is a cerebral vascular accident characterized by long-term impairments of motor function and activities of daily living (ADL) that affects approximately 10–15% of all patients with strokes (Sudlow et al., 1997). As of recently, it is strongly recommended that rehabilitative therapy (physical and occupational therapy) is started as

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Abbreviations: ICH, intracerebral hemorrhage; MDS, motor deficit score; PSD-95, postsynaptic density 95; SC, sham+control; ST, sham+treadmill; IC, ICH+control; IT, ICH+treadmill

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early as possible to improve their motor function and ADL (Johansson, 2000; Thorsén et al., 2005; Langhorne et al., 2005; Langhorne et al., 2007). Thus, early intervention for mobilization and training following stroke are well accepted clinically. A previous study indicated that early exclusive use of an affected limb exacerbates brain damage after focal brain ischemia (Risedal et al., 1999). However, many reports show the benefit of exercise at early stage. Early treadmill running after middle cerebral artery occlusion improved motor function and reduced infarct volume (Yang et al., 2003). Similarly, in an ICH model, early treadmill running induced recovery of motor function and reduction of lesion volume (Lee et al., 2003; 2005; Park et al., 2010). So, early treadmill running may have not only benefited motor function but also provided neuroprotection after ICH. However, the mechanisms of improved motor function by treadmill running after ICH are incompletely understood.

It is reported that neuronal plasticity contributes to the recovery of motor function after brain injury resulting from stoke or head trauma. Animal studies showed that the cellular and molecular events underlying spontaneous recovery after brain injury include structural changes in axons, dendrites, or synapses. Nguyen et al. (2008) reported that dendritic length and arborization increased in the contralateral striatum after ICH in rats. Furthermore, previous studies have shown that rehabilitation (enriched environment, reaching training of affected limb) improved motor function and enhanced changes in dendritic structure and complexity in the contralateral hemisphere after brain injury (Biernaskie et al., 2001; Jones et al., 1994; Bury et al., 2000). So, alterations of dendritic morphology in the contralateral hemisphere have been implicated in recovery of motor function after brain injury. Additionally, changes in synaptic activity as indicated by long-term potentiation (LTP) have been reported to contribute to brain reorganization after stroke. PSD-95, a synaptic scaffolding protein with multiple protein–protein interaction domains, is enriched in the postsynaptic density (PSD) and is an important regulator of synaptic strength and plasticity (Sheng et al., 2002; Han et al., 2008; Sheng et al., 2007). Previous studies have shown that running exercise induced changes in dendritic structure (Redila et al., 2006; Stranahan et al., 2007) and increased PSD-95 protein level (Dietrich et al., 2005; Hu et al., 2009) in normal rats. Therefore, running exercise is assumed to evoke brain plasticity. However, the effect of running exercise on dendritic morphology and PSD-95 protein level after ICH in rats has not been described.

The purpose of the present study was to investigate the effect of treadmill running on motor function and plastic changes in the striatum, focusing on dendritic morphology and PSD-95 protein level, after collagenase induced ICH in rats.

2. Results

2.1. Motor deficit score (MDS)

Animals had motor deficit after ICH that recovered over time. Furthermore, MDS of ICH+treadmill (IT) animals significantly improved compared with ICH+control (IC) animals by 15 days after ICH. Notably, there were significant differences between IT and IC animals at 7–15 days after ICH (7, 9–10 days, $p<0.05$; 8, 11–15 days, $p<0.01$. Fig. 1). MDS of each group were the same extent among experiments, such as H–E staining, Golgi-Cox staining and PSD-95 analysis.

2.2. Striatal volume loss

Striatal volume loss in ICH animals (IC, IT) was more than that of sham animals (sham+control, SC: sham+treadmill, ST) at 15 days after surgery ($p<0.05$). However, there were no significant differences between IT and IC animals (Fig. 2).

2.3. Alteration of dendritic morphology

In the ipsilateral striatum (Fig. 4A), IC animals had fewer intersections 140 μm from the cell body compared with ST animals ($p<0.05$). IT animals had fewer intersections 120 and 140 μm from the cell body as compared with ST animals ($p<0.05$). However, there were no significant differences between IT and IC animals. In the contralateral striatum (Fig. 4B), IC animals had a greater number of intersections 60 μm from the cell body compared with ST animals. IT animals had a greater number of intersections at 40, 60, and 80 μm from the cell body as compared with SC and ST animals ($p<0.05$). Furthermore, at 20 and 40 μm from the cell body, IT animals had a greater number of intersections compared with IC animals ($p<0.05$), (Fig. 3).

Total dendritic length in the ipsilateral striatum was not significantly different between groups (Fig. 5A). However, in the contralateral striatum, total dendritic length of IT animals was significantly longer than that of SC, ST and IC animals ($p<0.05$, Fig. 5B).

Spine density (number of spines/μm dendrite) was significantly lower in IC than SC and ST animals in the ipsilateral striatum ($p<0.05$), but there were no significant differences

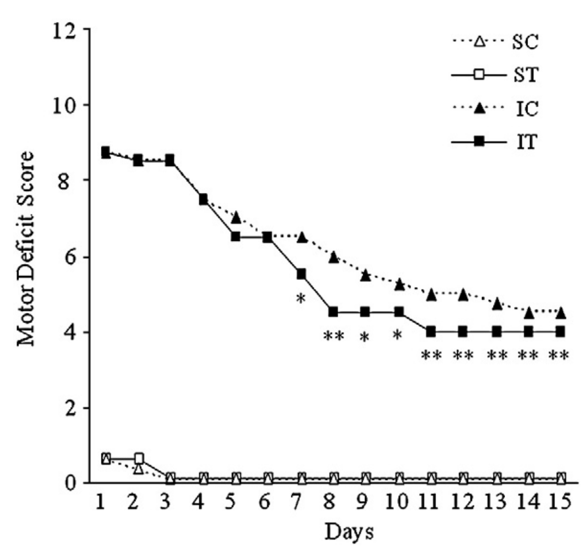

Fig. 1 – Change in motor deficit score (MDS) after ICH. Median values are shown. MDS of IT animals significantly improved compared with IC, especially between 7 and 15 days after ICH. $^{*}p<0.05$, $^{**}p<0.01$ compared with IC at each time point with Mann–Whitney *U*. SC: sham control group, ST: sham treadmill group, IC: ICH control group, IT: ICH treadmill group.