Motor Skills Training Enhances α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid Receptor Subunit mRNA Expression in the Ipsilateral Sensorimotor Cortex and Striatum of Rats Following Intracerebral Hemorrhage

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Background: We investigated the effects of acrobatic training (AT) on expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) subunits in the sensorimotor cortex and striatum after intracerebral hemorrhage (ICH). *Methods:* Male Wistar rats were divided into 4 groups: ICH without AT (ICH), ICH with AT (ICH + AT), sham operation without AT (SHAM), and sham operation with AT (SHAM + AT). ICH was induced by collagenase injection into the left striatum. The ICH + AT group performed 5 acrobatic tasks daily on days 4-28 post ICH. Forelimb sensorimotor function was evaluated using the forelimb placing test. On days 14 and 29, mRNA expression levels of AMPAR subunits GluR1-4 were measured by real-time reverse transcription-polymerase chain reaction. *Results:* Forelimb placing test scores were significantly higher in the ICH + AT group than in the ICH group. Expression levels of all AMPAR subunit mRNAs were significantly higher in the ipsilateral sensorimotor cortex of rats in the ICH + AT group than in that of rats in the ICH group on day 29. GluR3 and GluR4 expression levels were reduced in the ipsilateral striatum of rats in the ICH group compared with that of rats in the SHAM group on day 14. *Conclusions:* These changes may play a critical role in motor skills training-induced recovery after ICH. **Key Words:** Motor skills training—sensorimotor cortex—AMPA receptor—cortical plasticity—striatum.

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Introduction

Intracerebral hemorrhage (ICH) is associated with high rates of mortality and permanent morbidity. In survivors, serious motor and sensory deficits limit activities of daily living and severely impair quality of life.[1] Intensive rehabilitation starting soon after ICH is required to minimize or reverse these functional impairments and activity limitations. There are multiple approaches to physical rehabilitation after stroke. In animals, the effects of physical rehabilitation have been modeled using constraint-induced movement therapy, and treadmill running following experimental insults, including induced ICH.[2,3]

We have studied the influence of motor skills training on sensorimotor function following ICH in rats. In ischemic rats, motor skills training induces synaptogenesis in the sensorimotor cortex and improves motor performance compared with those by simple repetitive training.[4] Motor skills training can enhance synaptoplastic changes required to relearn movements of the affected limbs. Our previous study has demonstrated that motor skills training using "acrobatic" tasks improves or reverses motor dysfunction, enhances neural activity, and upregulates PSD95 protein expression in the sensorimotor cortex after ICH.[5]

PSD95 is a scaffolding protein necessary for the recruitment and stabilization of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors at postsynaptic sites apposed to glutamatergic boutons. Overexpression of PSD95 recruits AMPA receptors (AMPARs) to postsynaptic sites and enhances excitatory postsynaptic currents.[6] AMPARs are the predominant determinant of transmission strength at most glutamatergic synapses and thus are the major receptors responsible for expression of synaptic plasticity. Specifically, AMPARs are inserted into the postsynaptic membrane during long-term potentiation (LTP) and removed during long-term depression.[7] As LTP is activated by motor skills learning and contributes to network reorganization after a stroke,[8,9] enhanced AMPAR expression may underlie the recovery of motor function associated with rehabilitation. However, the influence of motor skills training following ICH on specific AMPAR subunit mRNA expression levels is unclear. An AMPAR is a heteromultimer of 4 subunits, GluR1, GluR2, GluR3, and GluR4, that confer specific kinetic properties to the functional channel and exhibit characteristic distribution patterns in the rat cerebrum.[10] This study examined the effects of our acrobatic training (AT) motor skills regimen[10] on AMPAR subunit mRNA expression levels in the sensorimotor cortex and striatum of rats following ICH.

Materials and Methods

Animals

Male Wistar rats (180-220 g, n = 48) were housed at 23 ± 1°C under a 12-h light-dark cycle with ad libitum access to food and water throughout the experiment. Animal care and surgical procedures were performed in accordance with the animal care guidelines of the Niigata University of Health and Welfare, Japan. Animals were randomly assigned to 4 groups: ICH + no training (ICH, n = 18), ICH + AT (n = 18), sham operation + no training (SHAM, n = 12), and sham operation + AT (SHAM + AT, n = 12). Six rats from each group were used for evaluation of mRNA expression on days 14 and 29, and lesion volume on day 29.

Surgery

ICH was induced as described previously.[5] Briefly, animals were anesthetized with sodium pentobarbital (45 mg/kg, intraperitoneal) and placed in a stereotaxic frame. ICH was induced by microinjection of 1.2 μL saline containing .24 U bacterial collagenase (Type IV; Sigma-Aldrich, St. Louis, MO) into the left striatum. The stereotaxic coordinates of the injection site were as follows: 3.0 mm lateral to the midline, .2 mm anterior to bregma, and 6.0 mm below the surface of the brain. The SHAM group was injected with .9% saline at the same coordinates.

Motor Skills Training

AT comprised 5 tasks (Fig 1), which involve a platform, rope, rope ladder, parallel bar, and barrier, previously demonstrated to restore motor learning following ICH.[7] Rats in the ICH + AT and SHAM + AT groups performed each task 4 times daily on days 4-28 post ICH.

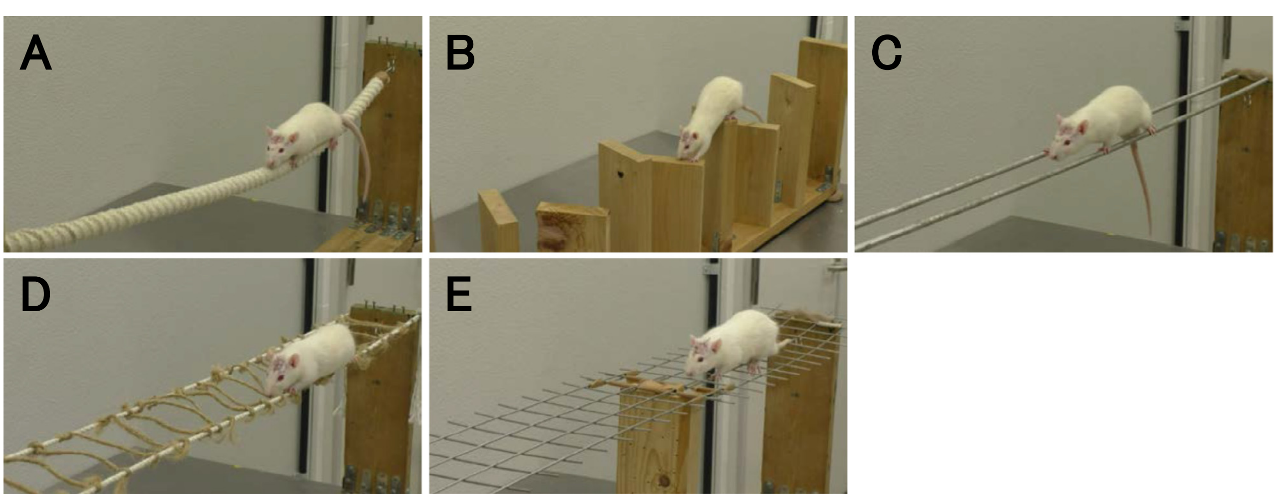

Figure 1. *The acrobatic training (AT) regimen. The rat was required to traverse a grating platform (A), parallel bar (B), rope (C), rope ladder (D), and barrier (E) from end to end. Each course was 1-minute long with a dark box at the end.*