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Effect of Inhibition of DNA Methylation Combined with Task-Specific Training on Chronic Stroke Recovery

In-Ae Choi [2], Cheol Soon Lee[2], Nayeon Ko[1], Dong-Hee Choi[2], Jongmin Lee[1,2*†]

Konkuk University School of Medicine and Konkuk University Medical Center, Department of Rehabilitation Medicine[1], Konkuk University, Center for Neuroscience Research, Institute of Biomedical Science and Technology[2]

Objective

To develop new rehabilitation strategies for chronic stroke, this study examined the effectiveness of task-specific training (TST) and TST combined with DNA methyltransferase inhibitor in chronic stroke recovery.

Methods

Rats underwent a photothrombosis surgery to impair the sensorimotor cortex. Eight weeks after stroke, animals were trained on the staircase test. 5-Aza-dC infusion was started on the contralesional hemisphere using an osmotic pump and lasted for 28 days after stroke. During 5-Aza-dC delivery, animals were exposed to TST for 4 weeks. Functional recovery was assessed using the staircase test, the cylinder test, and the modified neurological severity score (mNSS) every 2 weeks. A biotinylated dextran amine tracer was injected into the non-lesioned forelimb sensorimotor cortex at the end of behavioral test, to determine axonal plasticity in the corticospinal tract (CST). Expression of BDNF was determined by Western blotting on contralateral motor cortex tissues.

Results

TST and TST combined with 5-Aza-dC significantly improved the skilled reaching ability in the staircase test and ameliorated the mNSS scores and cylinder test performance. TST and TST with 5-Aza-dC significantly increased the crossing fibers from the contralesional red nucleus, reticular formation in medullar oblongata, and dorsolateral spinal cord. Mature BDNF was significantly upregulated by TST and TST combined with 5-Azd-dC. Functional recovery after chronic stroke may involve axonal plasticity and increased mature BDNF by modulating DNA methylation in the contralesional cortex. Conclusion

Our results suggest that combined therapy to enhance axonal plasticity based on TST and 5-Aza-dC constitutes a promising approach for promoting the recovery of function in the chronic stage of stroke.

Keywords

stroke; chronic stage; task-specific training; DNA methylation; axonal plasticity; functional recovery; mature brain-derived neurotrophic factor

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