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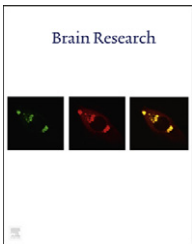

Research Report

Cortical electrical stimulation promotes neuronal plasticity in the peri-ischemic cortex and contralesional anterior horn of cervical spinal cord in a rat model of focal cerebral ischemia

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ABSTRACT

Purpose: This study evaluated the effect of cortical electrical stimulation (CES) on function recovery, dendritic plasticity, astrogliosis, and neuron recruitment in the peri-ischemic cortex (PIC) and contralesional anterior horn of cervical spinal cord (CSC) in a rat model of focal cerebral ischemia. *Materials and methods*: Rats were pre-trained on single pellet retrieval task, then received focal ischemic lesions and electrodes implantation. Seven days after surgery, rats received CES (CES group) or no stimulation (NS group) during 18 days of training. Behavior data on stimulation days 2, 4, 6, 8, 10, 12, 14, 16 and 18 were pooled for use. Immunohistochemical investigations for microtubule-associated protein 2 (MAP-2), glial fibrillary acidic protein (GFAP) and neuronal nuclei antigen (NeuN) were performed. *Results*: Rats in CES group showed greater functional recovery of the impaired forelimb compared to the NS group. Moreover, the functional improvement coincided with a significant increase in MAP-2-immunoreactive dendritic surface density in PIC and CSC ($P=0.011$; $P=0.005$, respectively). CES group had a significant decrease in GFAP-immunoreactive astrocytic surface density in PIC and CSC ($P=0.039$; $P=0.013$, respectively). In the immunoassaying of NeuN, there was no significant difference between the two groups in PIC and CSC ($P=0.834$, $P=0.782$, respectively). *Conclusion*: CES can promote dendritic plasticity and reduce astrogliosis in the PIC and CSC in a rat model of focal cerebral ischemia. CES is still an appealing method for post-stroke rehabilitation provided that viability of pathways is evaluated presurgically.

Abbreviations: CES, cortical electrical stimulation; MAP-2, microtubule-associated protein 2; GFAP, glial fibrillary acidic protein; NeuN, neuronal nuclei antigen; PIC, peri-ischemic cortex; CSC, contralesional anterior horn of cervical spinal cord

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1. Introduction

Stroke is the major cause of adult disability, resulting in residual impairments that diminish most stroke survivors' independence and quality of life (Nowak, 2008). Motor rehabilitative training can reduce these impairments but it is often insufficient to restore normal levels of function (Duncan et al., 2000; Dobkin, 2004). Searching for new effective methods to improve functional recovery is ongoing. Brain stimulation, as a means of directing adaptive plasticity, is appealing. Animal studies and Phase I and II trials in humans have indicated safety, feasibility, and efficacy of combining rehabilitation and concurrent invasive cortical stimulation (Plow et al., 2009). However, the Everest Clinical Trial, a recent Phase III trial, showing no advantage of the combination (Harvey and Winstein, 2009; Plow et al., 2009).

The findings of this Phase III trial seem surprising in light of positive findings in the previous studies. Plow et al. (2009) reviewed of factors that may contribute to this failure and they believed that insufficient viability of descending pathways is an important factor. Viability of descending pathways could be assessed intraoperatively by evoking movements using epidural electrodes. In the Phase I and II trials, 100% and 42% of patient in the combined treatment group showed evoked movements intraoperatively, respectively. However, Only 16% of patients in the Phase III trial showed evoked movements intraoperatively (Northstar, unpublished data, 2008; Plow et al., 2009).

In this study, we selected the ischemic rats with viability of descending pathways, which were demonstrated intraoperatively by using epidural electrodes, and then evaluate the effect of cortical electrical stimulation (CES) on dendritic plasticity, astrocyte activation and neuron recruitment in the peri-ischemic cortex and contralesional anterior horn of cervical spinal cord. We are trying to explain the reason behind the result from Phase III trial, and to figure out the indications for this new method.

2. Results

2.1. Behavioral evaluation

2.1.1. Single pellet retrieval task

As shown in Fig. 1, both groups had similar post-lesion declines in performance on the single pellet reaching task. CES during training significantly enhanced reaching performance over days of training relative to training alone. The group differences were significant by ANOVA analyses ($F=4.956$, $P=0.041$). The percent of successful retrievals of the CES group was significant higher than that of the NS group on days 14, 16 and 18 after treatment ($t=2.427$, $P=0.027$; $t=4.218$, $P=0.001$; $t=4.451$, $P<0.001$, respectively) by post-hoc analyses.

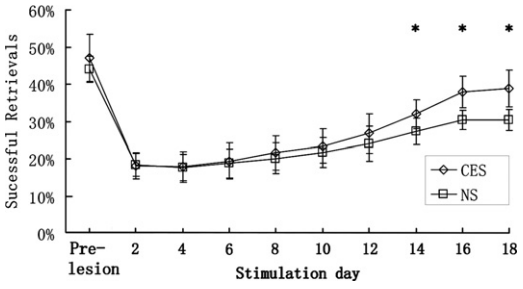

Fig. 1 – The performance on the single pellet reaching task in the CES and NS groups. *P<0.05, CES group significantly different from NS group.

2.1.2. Limb use asymmetry test

After ischemic lesion, the proportionate use of the dominant forelimb (impaired forelimb) reduced significantly (Fig. 2). Rats in the CES group returned to more symmetrical use of the forelimbs than NS group. By the end of stimulation, rats in CES group were performing at pre-lesion levels of performance whereas NS rats had more moderate improvements. The group differences were significant by ANOVA analyses ($F=4.528$, $P=0.049$). Limb use asymmetry score of the CES group was significantly higher than that of the NS on days 8, 16 and 18 after treatment ($t=2.605$, $P=0.019$; $t=2.929$, $P=0.01$; $t=3.505$, $P=0.003$, respectively) by post-hoc analyses.

2.2. Immunohistochemistry

2.2.1. MAP-2 staining in the peri-ischemic cortex (PIC) and contralesional anterior horn of cervical spinal cord (CSC)

In the ischemic boundary zone, MAP-2 immunostaining was rare in rats that received no stimulation treatment (Fig. 3A), while rats that received CES had greater surface density of MAP-2-immunoreactive dendrites in the peri-ischemic cortex (Fig. 3B). Statistical analysis (Fig. 3C) showed significantly higher surface density at peri-ischemic cortex in the CES group compared to the NS group ($P=0.011$).

The MAP-2-immunoreactive dendritic surface density in the CSC was similar to that in the PIC of the two groups. MAP-2 immunostaining in the CSC was rare in the NS group (Fig. 3D), while rats in CES group had greater MAP-2-immunoreactive dendritic surface density (Fig. 3E). Statistical analysis (Fig. 3F) showed significantly higher surface density at CSC in the CES group compared to the NS group ($P=0.005$).

2.2.2. GFAP staining in the PIC and CSC

In the ischemic boundary zone, GFAP immunostaining was rare in rats that received CES (Fig. 4A), while rats that received no stimulation treatment had greater GFAP-immunoreactive

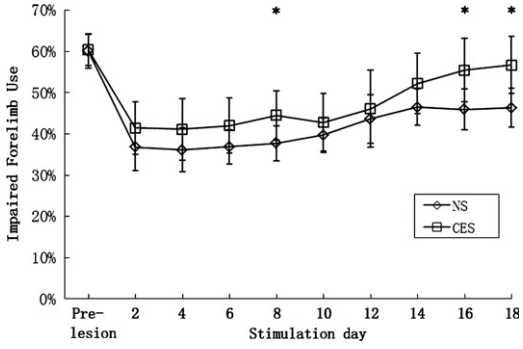

Fig. 2 – The limb use asymmetry scores in the CES and NS groups. * P < 0.05, CES group significantly different from NS group.