Brain Research 1662 (2017) 31–38

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/bres

Research report

Enhancement of brain plasticity and recovery of locomotive function after lumbar spinal cord stimulation in combination with gait training with partial weight support in rats with cerebral ischemia

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ARTICLE INFO

Article history:
Received 7 November 2016
Received in revised form 14 February 2017
Accepted 15 February 2017
Available online 22 February 2017

Keywords:
Stroke
Spinal cord stimulation
Rehabilitation
Recovery
Plasticity
Brain ischemia

ABSTRACT

Lumbar spinal cord stimulation (LSCS) is reportedly effective for the recovery of locomotive intraspinal neural network, motor cortex and basal ganglia in animals with complete spinal cord injury and parkinsonism. We evaluated the effect of LSCS in combination with gait training on the recovery of locomotive function and brain plasticity using a rat model of brain ischemia. Adult male Sprague Dawley rats with ischemia were randomly assigned into one of four groups: sham treatment (group 1), LSCS only (group 2), LSCS with gait training and 50% (group 3) and 80% (group 4) of body weight support. Evaluations before randomization and 4 weeks after intervention included motor scoring index, real-time PCR and Western blot. Motor scoring index was significantly improved after the intervention in groups 2 and 3. The ratio of phospho-protein kinase C (PKC) to PKC measured in the infarcted area tended to be higher in groups 3 and 4. Protein expression of mGluR2 and mRNA expression of mGluR1 measured in the contralateral cortex were lower in groups 3 and 4. The ratio of phospho-Akt to Akt and mRNA expression of vascular endothelial growth factor measured in the ischemic border zone were higher in group 2. The mRNA expression of MAP1b measured in the infarcted area was significantly higher in group 2. The findings suggest that LSCS and gait training with an adequate amount of body weight support may promote brain plasticity and facilitate the functional recovery.

1. Introduction

Rates of stroke mortality have decreased in the era of more refined acute care. Still, the absolute number of stroke survivors and the overall global burden of stroke continue to increase (Feigin et al., 2014). Facilitating recovery after stroke is an area of active research.

Recent studies have demonstrated lumbar spinal cord stimulation (LSCS) can promote locomotion. In a complete spinal transection rat model, LSCS can activate spinal cord central pattern generators and initiate locomotor activity with a specific amount of body weight support (Ichiyama et al., 2008, 2005; Lavrov et al., 2008). Stepping patterns are induced by sensory feedback related to weight bearing (Courtine et al., 2009; Grillner et al., 2008; Rossignol et al., 2006). Epidural electrical stimulation of the dorsal columns in the spinal cord promotes the recovery of locomotion in animal models of Parkinson's disease (Fuentes et al., 2010, 2009). In animal models of stroke, trials with cervical SCS, rather than LSCS have revealed that cervical SCS increases cerebral blood flow and may have a neuroprotective effect rather than a therapeutic effect (Hosobuchi, 1991; Matsui and Hosobuchi, 1989; Sagher et al., 2003). SCS is widely used clinically for severe pain control (Kumar and Rizvi, 2014; Nagel et al., 2014). However, the effect of LSCS in locomotion and brain plasticity has never been reported in animal models of stroke animals.

The objectives of the present study were to evaluate the effect of LSCS in combination with gait training and the influence of sensory afferent input using a specific amount of body weight support on the recovery of locomotion, and to reveal the underlying mechanism of functional recovery at the level of protein synthesis and gene expression on the assumption that LSCS can promote the recovery of locomotion using brain ischemia rat model.

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http://dx.doi.org/10.1016/j.brainres.2017.02.017
0006-8993/

2. Results

Eight of the 63 rats died (one in group 1; 3 in group 2; 2 in group 3; 2 in group 4) during the experimental procedure. Of the 8 rats with MCA occlusion, 2 (one each in group 2 and 3) died within the first 24 h because of overly large sized cerebral infarct that was evident upon autopsy. A rat in group 2 had to be killed because of a l > 25% decrease in body weight that occurred within a few days of electrode implant operation. One rat in group 4 died just after recovering from anesthetic for the electrode implant. Two rats (one each in group 1 and 2) died during the electrical stimulation. Two rats (one each in group 3 and 4) died during the treadmill training. Additionally, three rats were withdrawn from the study during the experimental procedure. One rat from group 2 was withdrawn because electrical stimulation was inadequately provided. The other 2 rats (both from group 2) had internal organ bleeding due to an unknown cause. Ten of the 52 rats were sacrificed to confirm that all procedures including MCAO procedures and electrode implant were made adequately. The remaining 42 rats completed the 4-week experimental course and their data were used for analysis.

2.1. Behavioral task

Neurological functional score on postoperative day 1 and at 4 weeks was obtained from the 42 adult male Sprague Dawley rats (250–320 g body weight). Mean of neurological functional score on postoperative day 1 after electrode implantation was 14.30 ± 2.00 in group 1, 13.44 ± 1.51 in group 2, 12.50 ± 1.31 in group 3, and 12.67 ± 1.12 in group 4. The 4-week score was 14.10 ± 2.08 in group 1, 15.22 ± 1.56 in group 2, 14.88 ± 1.96 in group 3 and 12.67 ± 1.12 in group 4. The difference in neurological functional score between post-electrode implantation and 4 weeks after intervention was significantly higher in the LSCS only group and LSCS with 50% support gait training groups (−0.20 ± 1.15 in group 1, 1.78 ± 2.05 in group 2, 2.38 ± 1.30 in group 3, 0.00 ± 0.87 in group 4, $p < 0.001$) (Fig. 1A.).

2.2. Western blot

The ratio of phopho-PKC to PKC measured in the infarcted area tended to be higher in the LSCS with 50% and 80% body weight support gait training groups (1.43 ± 1.71 and 1.75 ± 2.30, respectively) than that in other groups (0.66 ± 0.31 in group 1, 0.70 ± 0.18 in group 2). Increased level of phopho-PKC implies increased neuronal excitability and brain plasticity (Chakravarthy et al., 1998; Durkin et al., 1996). The ratio of phospho-protein kinase B (p-Akt) to Akt tended to be higher in the LSCS only group (2.89 ± 3.21 in ischemic border zone and 1.42 ± 1.67 in contralateral cortex) than that in other groups in ischemic border zone (1.21 ± 1.03 in group 1, 0.70 ± 0.42 in group 3 and 0.82 ± 0.51 in group 4) and contralateral cortex (0.44 ± 0.71 in group 1, 0.37 ± 0.58 in group 3 and 0.29 ± 0.40 in group 4). Akt is related to neurogenesis and angiogenesis (Shioda et al., 2009). The contralateral cortex protein expression level of mGluR2 which is related to excitotoxicity (Blaabjerg et al., 2003), was significantly lower in LSCS with 50% and 80% body weight support gait training groups (0.74 ± 0.17 in group 1, 0.86 ± 0.16 in group 2, 0.49 ± 0.15 in group 3 and 0.47 ± 0.21 in group 4; $p = 0.049$; Fig. 1B.)

2.3. RT-PCR

The contralateral cortex mRNA expression of mGluR1, which is related to excitotoxicity (Pellegrini-Giampietro, 2003), tended to be lower in LSCS with 50% and 80% support gait training groups than in the other groups. (0.12 ± 0.04 in group 1, 0.13 ± 0.04 in group 2, 0.07 ± 0.06 in group 3 and 0.06 ± 0.06 in group 4), although the difference was marginally significant ($p = 0.088$).Also, mRNA expression in the ischemic border zone of VEGF, which is related to neurogenesis and angiogenesis (Jin et al., 2002; Kaya et al., 2005; Nowacka and Obuchowicz, 2012), was significantly higher in LSCS only group than the other groups. (1.82 ± 1.55 in group 1, 5.20 ± 0.99 in group 2, 2.58 ± 0.48 in group 3 and 2.43 ± 1.83 in group 4; $p = 0.043$). In the infarct area mRNA expression of MAP1b, which is related to neurogenesis (Book et al., 1996; Calvert et al., 1987; Gordon-Weeks, 1993), was significantly higher in the LSCS only group. (1.16 ± 0.31 in group 1, 1.58 ± 0.35 in group 2, 0.95 ± 0.30 in group 3 and 0.79 ± 0.28 in group 4; $p = 0.028$; Fig. 1C.) However, mRNA expression for other primers did not differ between groups.

3. Discussion

The findings of this study demonstrated epidural spinal stimulation at the L2 and S1 level and gait training with a specific amount of body weight support facilitated the recovery of locomotor ability in rats with MCA occlusion. The recovery shown here correlated with the change of brain plasticity assessed by western blot and RT-PCR analysis.

3.1. Why is the amount of body weight support important in facilitating locomotion?

In the present study, hindlimb stepping patterns were observed only when the rats bore 50–80% of their body weight. Less or more weight bearing did not produce locomotor activities in response to stimulation. A certain amount of body weight bearing provides the proprioceptive input and dynamic sensory afferent information from periphery to locomotive modulation for the entire stepping process (Courtine et al., 2007). We examined the effect of the difference in the amount of body weight support based on the previous literatures that showed the amount of afferent sensory input affects the recovery of local intraneural circuits after spinal cord injury (Grillner, 2003; Grillner et al., 1981, 2008; Grillner and Wallen, 1985; Rossignol et al., 2006). Also, a support for providing a minimal lateral stability is necessary for locomotion (Leblond et al., 2003).

3.2. Neural control of locomotion via the exchange of information between the brain and the spinal cord

Supraspinal injury such as a stroke does not allow to communicate information between the brain and the spinal cord. In the absence of adequate supraspinal input to the lumbosacral spinal cord, generating the rhythm for locomotion requires the essential control made at the spinal cord level combined with the afferent input from the moving lower limbs (Courtine et al., 2007). Sensory input from the periphery works together with the spinal circuits responsible for central pattern generation to modulate locomotion (de Leon et al., 2001; Edgerton et al., 2001, 1991). The recovery of locomotion results from these processes and from facilitated brain plasticity.

3.3. Task oriented training in the recovery of locomotion

Although the results from this study could not show the additional effect of gait training plus epidural SCS measured with behavioral functional score, we hypothesized that task oriented training, such as gait training with body weight support, promotes recovery. Treadmill exercise is known to facilitate the functional recovery and neuroprotection in a rat model of ischemic stroke (Kim and Kim, 2013; Nudo et al., 1996; Sun et al., 2013). Findings