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Research Report

Does treatment with bone marrow mononuclear cells recover skilled motor function after focal cortical ischemia? Analysis with a forelimb skilled motor task in rats

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ABSTRACT

Previous studies have shown sensorimotor recovery by treatment with bone marrow mononuclear cells (BMMCs) after focal brain ischemia. However, sensorimotor tests commonly used are designed to examine motor patterns that do not involve skill or training. We evaluated whether BMMCs treatment was able to recover forelimb skilled movements. Reaching chamber/pellet retrieval (RCPR) task was used, in which animals had to learn to grasp a single food pellet and lead it to its mouth. We also evaluated therapeutic effect of this training on unskilled sensorimotor function. Adult male Wistar rats suffered unilateral cortical ischemia by thermocoagulation in motor and somesthetic primary areas. A day later, they received i.v. injection of 3×10^7 BMMCs or vehicle (saline), forming four experimental groups: BMMCs+RCPR; saline+RCPR; BMMCs and saline. Cylinder and adhesive tests were applied in all experimental groups, and all behavioral tests were performed before and along post-ischemic weeks after induction of ischemia. Results from RCPR task showed no significant difference between BMMCs+RCPR and saline+RCPR groups. In cylinder test, BMMCs-treated groups showed significant recovery, but no significant effect of RCPR training was observed. In adhesive test, BMMCs treatment promoted significant recovery. Synergistic effect was found since only together they were able to accelerate recovery. The results showed that BMMCs treatment promoted increased recovery of unsophisticated sensorimotor function, but not of skilled forepaw movements. Thus, BMMCs might not be able to recover all aspects of sensorimotor functions, although further studies are still needed to investigate this treatment in ischemic lesions with different locations and extensions.

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Abbreviations: ANOVA, analysis of variance; BMMCs, bone marrow mononuclear cells; MSCs, mesenchymal stem cells; PBS, phosphate-buffered saline; PID, post-ischemic day; RCPR, reaching chamber/pellet retrieval; SEM, standard error mean; TTC, 2,3,5-triphenyltetrazolium chloride

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1. Introduction

Bone marrow-derived cells have been shown to have beneficial properties for treatment of brain ischemia (Maltman et al., 2011; Mendez-Otero et al., 2007; Mezey, 2007). Although they have been described as multipotent cells, with supposed capability to regenerated some lost tissue cells (Crain et al., 2005; Krause et al., 2001; Shyu et al., 2006), their main mechanisms of action has been shown to be chemoattraction to lesioned tissues and release of several cytokines and trophic factors (Maltman et al., 2011; Shyu et al., 2006; Takahashi et al., 2006). The use of bone marrow-derived mesenchymal stem cells (MSCs) has been extensively shown as a promising therapeutic approach (Maltman et al., 2011). However, therapeutic use of MSC involves cell cultivation for several weeks, which hinders autologous transplantation in the acute phase of brain ischemia, when treatment should be more successful. Alternatively, some studies have used bone marrow mononuclear cells (BMMCs), a cell fraction that contains MSCs, hematopoietic stem cells, hematopoietic progenitor cells and endothelial progenitor cells (Orkin, 2000; Wang et al., 2008; Weissman et al., 2001). BMMCs can be harvested in 1.5–6 h and autologously administrated without any previous cultivation (Battistella et al., 2011; Brenneman et al., 2010; Iihoshi et al., 2004; Savitz et al., 2011), which allows treatment during the acute phase (Mendez-Otero et al., 2007). Indeed, BMMCs has been shown to be as beneficial as MSCs to treat acute brain ischemia in animal models (de Vasconcelos dos Santos et al., 2010; Giraldi-Guimarães et al., 2009; Iihoshi et al., 2004; Kamiya et al., 2008; Yang et al., 2011).

Several previous reports have demonstrated induction of functional recovery by MSCs and BMMCs in sensorimotor tests using different models of brain ischemia (Chopp and Li, 2002; de Vasconcelos dos Santos et al., 2010; Giraldi-Guimarães et al., 2009; Iihoshi et al., 2004; Kamiya et al., 2008; Yang et al., 2011). However, functional tests usually applied to evaluate treatment-induced improvements of sensorimotor function after brain ischemia involves unsophisticated motor patterns of limbs, which do not require skill and previous training to be performed (e.g., spontaneous postural support, flexion, placing during locomotion, balance and tactile response) (Schaar et al., 2010; Schallert, 2006). Although recovery of these motor patterns should represent significant functional outcome, functional analyses should be extended to evaluate whether cell therapies are also able to promote recovery of skilled movements. Unlike previously thought, rat skilled forepaw movements has been shown to be similar to primate hand movements, having single digit movements controlled by motor cortex (Alaverdashvili and Whishaw, 2008). The measurement of success in grasping is one of the most used approaches to evaluate loss and recovery of skilled movement of forepaw after brain ischemia (Biernaskie et al., 2005; Bury and Jones, 2002; Conner et al., 2003; Grabowski et al., 1993; Zai et al., 2009).

We have previously shown sensorimotor recovery of impaired forelimb after treatment with BMMCs in a model of unilateral focal cortical ischemia. We used functional tests that do not require training and evaluate unsophisticated forelimb movements (de Vasconcelos dos Santos et al., 2010; Giraldi-Guimarães et al., 2009), i.e., cylinder and adhesive tests (Schaar et al., 2010; Schallert, 2006). Here, we extended the functional analysis of the same model of ischemia using the "reaching chamber/pellet retrieval" (RCPR) task (Schaar et al., 2010). We evaluated the effectiveness of the BMMCs treatment on the skilled movement of grasping with forepaw after unilateral focal cortical ischemia. Furthermore, skilled training has been shown to promote cortical motor map reorganization and enhancement of lesion-induced structural plasticity in motor cortex (Jones et al., 1999; Kleim et al., 1998, 2004). Since the RCPR task involves preischemic training and a high frequency of testing after ischemia, we also evaluated a possible effect of the RCPR training, alone and associated to the BMMCs treatment, on the performance in sensorimotor tests previously studied in the same model of ischemia (de Vasconcelos dos Santos et al., 2010; Giraldi-Guimarães et al., 2009).

2. Results

2.1. *Thermocoagulatory ischemic lesion and lesion volume*

The protocol of cortical ischemia by thermocoagulation has been shown to induce a focal lesion subjacent to the affected

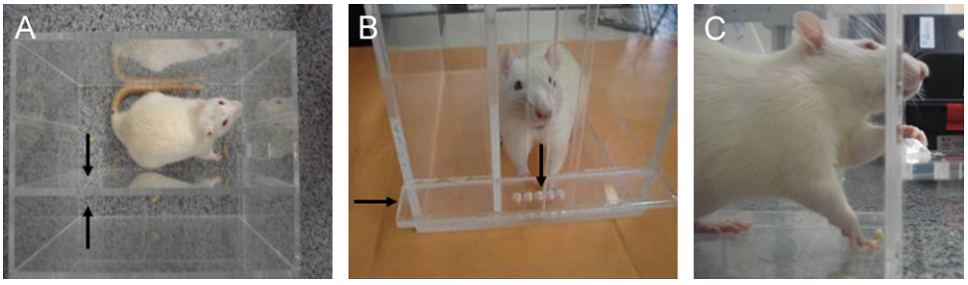

Fig. 1 – Images of the plexiglass box used for RCPR task: (A) upper view of the box showing a removable wall (arrows) inside the box. It served as a barrier to prevent the use of the forelimb opposite to this wall, during pellet retrieval by the front window (in the right side of the image). (B) Front view showing the front window and the external platform (arrow pointing to the side). Note the holes located in front of frontal window, where food pellets can be placed (arrow pointing downwards). (C) Lateral view showing a rat extending its left forelimb through the front window. Note the presence of a shield on the platform, attached in the opening of the front window, whose purpose is to prevent the animal just push the pellet into the box, being obliged to grasp and lift it.

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