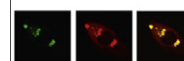


Available online at www.sciencedirect.com

SciVerse ScienceDirect

www.elsevier.com/locate/brainres

Brain Research



Research Report

Different routes of administration of human umbilical tissue-derived cells improve functional recovery in the rat after focal cerebral ischemia

Li Zhang^{a,*}, Yi Li^a, Michael Romanko^b, Brian C. Kramer^c, Anna Gosiewska^c, Michael Chopp^{a,d}, Klaudyne Hong^c

^aDepartment of Neurology, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI 48202, United States

^bTunnel Government Services, Bethesda, MD, United States

^cAdvanced Technologies and Regenerative Medicine, LLC a Johnson & Johnson Company, PO Box 151, US 22 West, Somerville, NJ 08876, United States

^dDepartment of Physics, Oakland University, Rochester, MI 48309, United States

ARTICLE INFO

Article history:

Accepted 8 October 2012

Available online 12 October 2012

Keywords:

Cell transplantation

Focal cerebral ischemia

Plasticity

Rat model

ABSTRACT

Human umbilical tissue-derived cells (hUTC) are a potential neurorestorative candidate for stroke treatment. Here, we test the effects of hUTC treatment in a rat model of stroke via various routes of administration. Rats were treated with hUTC or phosphate-buffered saline (PBS) via different routes including intraarterial (IA), intravenous (IV), intra-cisterna magna (ICM), lumbar intrathecal (IT), or intracerebral injection (IC) at 24 h after stroke onset. Treatment with hUTC via IV and IC route led to significant functional improvements starting at day 14, which persisted to day 60 compared with respective PBS-treated rats. hUTC administered via IA, ICM, and IT significantly improved neurological functional recovery starting at day 14 and persisted up to day 49 compared with PBS-treated rats. Although IA administration resulted in the highest donor cell number detected within the ischemic brain compared to the other routes, hUTC treatments significantly increased ipsilateral bromodeoxyuridine incorporating subventricular zone (SVZ) cells and vascular density in the ischemic boundary compared with PBS-treated rats regardless of the route of administration. While rats received hUTC treatment via IA, IV, IC, and ICM routes showed greater synaptophysin immunoreactivity, significant reductions in TUNEL-positive cells in the ipsilateral hemisphere were observed in IA, IV, and IC routes compared with PBS-treated rats. hUTC treatments did not reduce infarct volume when compared to the PBS groups. Our data indicate that hUTC administered via multiple routes provide therapeutic benefit after stroke. The enhancement of neurorestorative events in the host brain may contribute to the therapeutic benefits of hUTC in the treatment of stroke.

© 2012 Elsevier B.V. All rights reserved.

*Corresponding author. Fax: +1 313 9161318.

E-mail address: lzhang@neuro.hfh.edu (L. Zhang).

1. Introduction

Stroke is a devastating neurological disorder which results in irreversible brain damage. Although acute thrombolysis with tPA improves stroke prognosis, therapeutic interventions aimed at promoting neurorestoration are still lacking. Cell-based therapy is emerging as a promising neurorestorative intervention for the treatment of stroke (Chen et al., 2001; Grabowski et al., 1993; McKay, 1997; Savitz et al., 2002; Zhao et al., 2002). By using various cell infusion regimens, we and others have demonstrated that cells isolated from a variety of sources can evoke restorative events and improve functional outcome in the experimental stroke (Chen et al., 2001, 2003; Chopp and Li, 2008; Grabowski et al., 1993; McKay, 1997; Savitz et al., 2002). The human umbilical cord is one of the most convenient sources of therapeutic cells. Human umbilical tissue-derived cells (hUTC) are capable of secreting several neurotrophic factors and cytokines and are a potential candidate for neurorestorative therapy (Alder et al., 2012; Lund et al., 2007). In the experimental stroke, we have previously demonstrated that intravenous administration of hUTC exerts potent neurorestorative effects and effectively improves neurological functional recovery in rats after stroke (Zhang et al., 2011). Thus, hUTC represents an attractive candidate for stroke therapy.

Many cell delivery strategies are being investigated for neurorestorative treatment in experimental neurodegenerative diseases, and each has its own advantages and potential drawbacks. Systemic administration such as intravenous (IV) and intraarterial (IA) injections are minimally invasive approaches for cell transplantation after ischemic stroke, with IV injection as the least invasive and most convenient route of administration. However, donor cells can be entrapped by the systemic organs, which may lead to low numbers of cell engraftment at ischemic lesion site (Chen et al., 2001; Kraitichman et al., 2005). IA injection can overcome the initial cell uptake by the systemic organs, which enable a broad distribution of donor cells in the immediate vicinity of ischemic tissue (Li et al., 2010; Walczak et al., 2008). However, IA has a potential for microembolization, which may

have detrimental effects on stroke outcome (Parr et al., 2007). Intrathecal injection such as intra-cisterna magna (ICM) and lumbar intrathecal (IT) deliver donor cells into the cerebral spinal fluid (CSF) stream, which enable a direct contact between donor cells and the surface of the brain. However, donor cells may have low survival rates due to the low nutrient content of the CSF (Brown et al., 2004). Intraparenchymal (IC) transplantation can bypass the blood-brain barrier, which directly deliver the donor cells to ischemic site (Koh et al., 2008). However, the invasive nature of the procedure may hamper its clinical application. Importantly, emerging data suggests that cell delivery route may influence the therapeutic efficacy of cell therapy. A previous study comparing intravenous versus intrastriatal cord blood administration in a rodent model of stroke revealed that behavioral recovery was similar with both striatal and femoral vein umbilical cord cell delivery; however, intravenous delivery was more effective than striatal delivery in producing long-term functional benefits to the stroke-induced animal (Willing et al., 2003). In another study, while rats subjected to intracerebral transplantation of human bone-marrow-derived CD133+ cells at 7 days after stroke exhibited profound functional improvement, intravenous delivery failed to improve neurological functional (Borlongan et al., 2005). However, to our knowledge, the feasibility and comparison of various routes of administration of one cell type in experimental stroke have not been comprehensively evaluated, side-by-side in one study. Thus, the present study compared the effects of the routes of administration of hUTC on neurological functional outcomes, following focal cerebral ischemia in rats using five different routes of administration.

2. Results

2.1. Neurological functional outcome

All rats exhibited severe deficits 1 day after transient middle cerebral artery (tMCA) occlusion with no significant differences measured by modified neurological severity score (mNSS) and adhesive removal test among the groups (Fig. 1). However, as

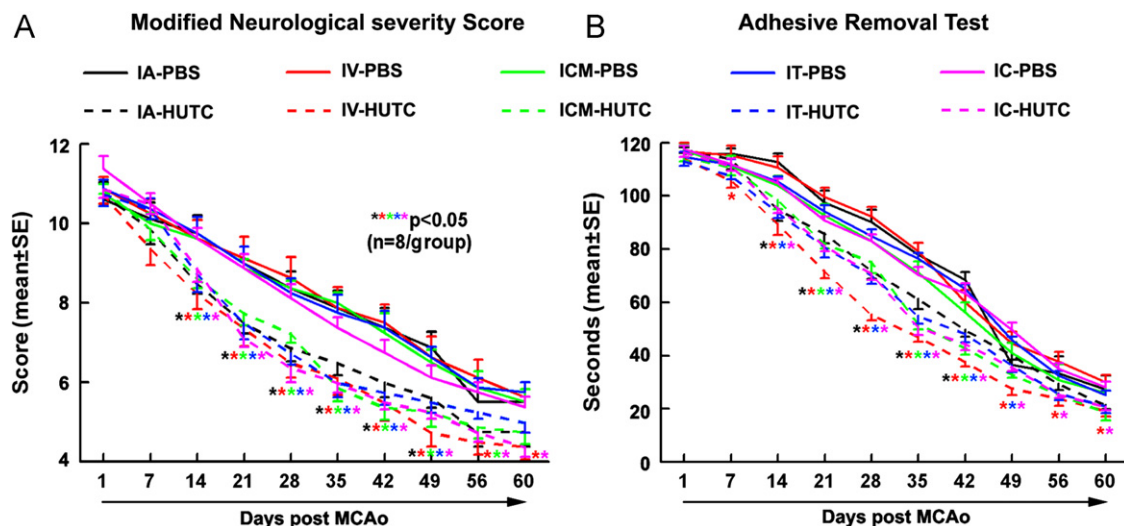


Fig. 1 – The effects of hUTC on neurological outcome. Panels A and B show temporal profiles of mNSS (A) and adhesive-removal test (B) during 60 days after stroke. * $p < 0.05$ as compared with the PBS groups ($n = 8/\text{group}$).

Download English Version:

<https://daneshyari.com/en/article/6264082>

Download Persian Version:

<https://daneshyari.com/article/6264082>

[Daneshyari.com](https://daneshyari.com)