BRAIN RESEARCH 1594 (2015) 267–273

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Brain Research

Research Report

Administration of human platelet-rich plasma reduces infarction volume and improves motor function in adult rats with focal ischemic stroke

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ARTICLE INFO

Article history:
Accepted 18 October 2014
Available online 6 November 2014

Keywords:
Biomaterials
Neuroprotection
Stroke
Therapeutics
Platelets
Albumin

ABSTRACT

Platelet-rich plasma (PRP) is a milieu of bioactive factors, including platelet derived growth factor, transforming growth factor beta, among many others. Despite accumulating evidence on PRP's safety and efficacy for treating musculoskeletal injuries, limited studies have been performed using PRP in brain disorders. This study aimed to explore the potential benefits of administration of human PRP lysate after ischemic stroke in rats. An ischemic stroke model was generated by occlusion of the right middle cerebral artery, then 90 min later, stroke rats were randomly assigned to receive local infusion to the ischemic area of human PRP lysate, human albumin solution (HSA), saline or no treatment at all. An additional group of stroke rats received systemic infusion of human PRP lysate to further assess the therapeutic effects of this treatment. Results showed that while local infusion of HSA or saline, and systemic administration of human PRP lysate, compared to no treatment significantly reduced infarct volume (37.4%, 40.1%, and 39.9% vs 49.7%) and neurological deficit score (2.2, 2.6, and 2.8 vs 3.7), the greatest neuroprotection (31.0% infarct volume and 1.6 neurological deficit score) was found in stroke animals that received local intra-arterial infusion of human PRP lysate (p's < 0.05). In conclusion, administration of human PRP attenuates brain injury after focal ischemia. Our results suggest PRP should be investigated further as a potential point-of-care biomaterial following stroke.

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http://dx.doi.org/10.1016/j.brainres.2014.10.035
0006-8993/

1. Introduction

Ischemic stroke is a leading cause of death and disability in adults worldwide. So far, the only specific treatment of acute ischemic stroke is recanalization of the occluded blood vessels with recombinant tissue plasminogen activator (rt-PA). Due to the limitations of available neuroprotective agents, the early treatment of stroke is of high research emphasis.

Platelet-rich plasma (PRP) is a biomaterial rich in cytokines and growth factors (GFs), which can be manufactured in an autologous manner and is effective in various models of sports medicine (Intini, 2009; Moraes et al., 2013), plastic surgery (Willemsen et al., 2013), myocardial infarction (Cheng et al., 2012), and peripheral nerve injury (Yu et al., 2011). However, the potential utility of PRP in ischemic stroke has yet to be tested. Our hypothesis that PRP may ameliorate brain function after ischemic stroke was based on the following reasoning: 1) our former work using local infusion of human albumin solution in ischemic rats proved to be safe and effective (Chen et al., 2013), and PRP is composed mainly of human serum albumin (HSA), thus providing us a rationale to test the feasibility to administer PRP through intra-arterial infusion; and 2) unlike HSA, PRP can provide biological support by secreting various neuroprotective and neurotrophic GFs including platelet derived growth factor (PDGF), transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), epithelial growth factor (EGF) (Boswell et al., 2012). There are three major biological processes implicated in neural repair, namely angiogenesis, neurogenesis, and synaptic plasticity which have been documented to occur in adult rat brains in response to injury, but also could be stimulated through cell-based therapies (Font et al., 2010). To this end, platelet derived GFs may enhance neurogenesis, modulate synaptic plasticity, positively affect neurite growth, branching and elimination, altogether may confer superior efficacy than HSA in affording functional recovery following ischemic injury. In the present study, we investigated the potential benefit of intra-arterial infusion of PRP lysate in a rat model of ischemic stroke.

2. Results

2.1. Growth factor production in PRP lysate

A centrifuge spin of 200 g for 6 min achieved platelet enrichment from whole blood by 185%, from 234.6±10.3 to 432.0±14.9 (platelets ×10\widehat9/L peripheral blood) (Table 1). The final platelet concentration of our plasma production met the Red Cross definition of PRP (>200 ×10 \widehat9 platelets/L) (Boswell et al., 2012).

It has been demonstrated that GFs are released from platelets in native (rather than recombinant) form and presumably in a biologically relevant ratio (Foster et al., 2009). PDGF-BB and TGF-β1 were chosen as representative GFs because of their demonstrated close association with PRP. Accordingly, GF levels of each PRP lysate sample from five donors were determined by ELISA. The mean levels of PDGF-BB and TGF-β1 were 10.70±0.995 (ng/mL) and 48.32±2.79 (ng/mL), respectively, while the same growth factors in HSA were -0.55±0.001 (ng/mL) and 1.85±0.696 (ng/mL) (Fig. 1).

2.2. Physiological parameters

There were no significant differences with respect to blood pH, PCO_2, and mean arterial pressure among the local treatment groups (Table 2). Local PRP lysate treatment significantly elevated PO_2 levels compared with stroke without treatment ($P<0.05$). As for the blood glucose levels, since the rats were non-fasting, the notable individual differences were expected, and the significant increase seen in both the local saline group and the local HSA group after MCA occlusion held no practical implications. Body temperature was maintained at ≈37 °C.

2.3. Infarct volume and neurological deficit

At 24 h after reperfusion, brain infarct volume was detected. ANOVA revealed significant treatment effect ($P<0.01$). Infarct volume in the stroke without treatment group was 49.7±1.8% ($n=9$). The local saline group (40.1±1.7%, $n=10$), local HSA group (37.4±2.1%, $n=10$) and systemic PRP lysate group (39.9±3.0%, $n=9$), which did not significantly differ among themselves, but were significantly reduced compared with stroke animals that received no treatment ($P<0.01$). The local PRP lysate group showed the greatest decrease in infarct volume (31.0±2.7%, $n=10$), which was significantly reduced compared to no treatment group, but even when compared with local saline group, local HSA group or systemic PRP lysate group ($P<0.05$) (Fig. 2).

At 30 min after reperfusion, ischemic animals demonstrated apparent neurological deficits with no significant difference between groups (score of 3.9±0.3, and 4.0±0.3, and 3.7±0.3, and 3.9±0.2, and 3.8±0.2) (Fig. 3). At 24 h after reperfusion, stroke rats in the no treatment group maintained a high neurological deficit score (3.7±0.2). All of the treatment groups including local saline group (2.6±0.2), local HSA group (2.2±0.3), local PRP lysate group (1.6±0.2), and systemic PRP lysate group (2.8±0.1) displayed significantly reduced neurological deficits compared to those stroke animals with no treatment ($P<0.01$). Interestingly, stroke rats in the local PRP lysate group showed a much further reduction of neurological deficits when compared with the other treatment groups ($P<0.05$) (Fig. 3).

Table 1 – Platelets yields (platelets X10\widehat9/L).

g Force/Time	Volunteer 1	Volunteer 2	Volunteer 3	Volunteer 4	Volunteer 5	Mean±SEM
Whole blood	215	255	254	244	205	234.6±10.3
200 g, 6 min	425	460	472	414	390	432.0±14.9