Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Brain Research

Research Report

Vasoactive intestinal peptide administration after stroke in rats enhances neurogenesis and improves neurological function

Jie Yang[a,*], *Qing-Dong Shi*[b], *Yuan-Bo Yang*[c], *Yi-Hua Qian*[a], *Gai-Feng Feng*[a], *Ling Chang*[d], *Chang-Hong Zong*[a]

[a]*Department of Human Anatomy, Histology and embryology, School of Basic Medical Sciences, Xi'an Jiaotong University Health Science Center, Xi'an, Shaanxi 710061, China*
[b]*Department of Critical Care Medicine, The First Affiliated Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi 710061, China*
[c]*Emergency Department, NO. 1 Hospital of Xi'an City, Xi'an, Shaanxi 710002, China*
[d]*Xi'an Electronic Engineering Research Institute, Xi'an, Shaanxi 710100, China*

ARTICLE INFO

Article history:
Accepted 1 September 2015
Available online 9 September 2015

Keywords:
Vasoactive intestinal peptide
Neurogenesis
Angiogenesis
Cerebral infarction
Vascular endothelial growth factor
Functional recovery
Middle cerebral artery occlusion

ABSTRACT

The aim of this study was to investigate the effects of vasoactive intestinal peptide (VIP) on neurogenesis and neurological function after cerebral ischemia. Rats were intracerebroventricular administered with VIP after a 2 h middle cerebral artery occlusion (MCAO) and sacrificed at 7, 14 and 28 days after MCAO. Functional outcome was studied with the modified neurological severity score. The infarct volume was evaluated via histology. Neurogenesis, angiogenesis and the protein expression of vascular endothelial growth factor (VEGF) were measured by immunohistochemistry and Western blotting analysis, respectively. The treatment with VIP significantly reduced the neurological severity score and the infarc volume, and increased the numbers of bromodeoxyuridine (BrdU) immunoreactive cells and doublecortin immunoreactive area in the subventricular zone (SVZ) at 7, 14 and 28 days after ischemia. The cerebral protein levels of VEGF and VEGF expression in the SVZ were also enhanced in VIP-treated rats at 7 days after stroke. VIP treatment obviously increased the number of BrdU positive endothelial cells in the SVZ and density of cerebral microvessels in the ischemic boundary at 28 days after ischemia. Our study suggests that in the ischemic rat brain VIP reduces brain damage and promotes neurogenesis by increasing VEGF. VIP-enhanced neurogenesis is associated with angiogenesis. These changes may contribute to improvement in functional outcome.

Abbreviations: BrdU, bromodeoxyuridine; PACAP, pituitary adenylate cyclase-activating polypeptide; MCAO, middle cerebral artery occlusion; NSPCs, neural stem/progenitor cells; SGZ, subgranular zone; SVZ, subventricular zone; VEGF, vascular endothelial growth factor; VIP, vasoactive intestinal peptide

*Corresponding author.
E-mail address: yangjie@mail.xjtu.edu.cn (J. Yang).

http://dx.doi.org/10.1016/j.brainres.2015.09.001
0006-8993/

1. Introduction

Cerebral ischemia results in a rapid onset of neurological injury due to occlusion of blood supply to the brain. The repair of infarct damage and the improvement of functional recovery are considered important strategic approaches for the treatment of stroke. Neural stem/progenitor cells (NSPCs) exist in two germinal centers in the adult brain: the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the hippocampal dentate gyrus (Gage, 2000). Cerebral ischemia induces NSPC proliferation in the SVZ and SGZ (Ohab et al., 2006; Zhang et al., 2005). Newly generated NSPCs can migrate into ischemic regions, where they may differentiate into mature neuron and participate in recovery from neurological deficit (Yamashita et al., 2006; Zhang et al., 2005). Substantial studies have documented that several growth and trophic factors can modulate ischemia-induced neurogenesis (Dibajnia and Morshead, 2013). Vascular endothelial growth factor (VEGF) is one of these factors that induces angiogenesis and is implicated in the process of neurogenesis after cerebral ischemia (Li et al., 2011; Sun et al., 2003; Wang et al., 2007). Studies of recent years have revealed that many endogenous neuropeptides play a regulatory role in neurogenesis (Zaben and Gray, 2013).

Vasoactive intestinal peptide (VIP) is a member of the pituitary adenylate cyclase-activating polypeptide (PACAP), secretin, and glucagon peptide family. In the nervous system, VIP is expressed by neurons where this neuropeptide, through specific membrane receptors: VPAC receptors (VPAC1 and VPAC2) showing similar affinities for VIP and PACAP, and PAC1 receptor having higher affinity for PACAP than VIP, exert pleiotropic effects including those on immunomodulation, muscle relaxation, cell proliferation and differentiation (Brenneman, 2007; Moody et al., 2003). Several studies have documented a robust neuroprotection of VIP in a variety of brain injury models (Brenneman, 2007; Moody et al., 2003; Yang et al., 2011) and a proangiogenic role in ischemic insult in vitro and in vivo (Yang et al., 2009, 2013). In addition, VIP is also a known modulator of developmental neurogenesis affecting the development of the neural tube (DiCicco-Bloom, 1996). In vitro, the neuropeptide has been found to regulate proliferation and differentiation of embryonic and neural stem cells (Mercer et al., 2004; Chafai et al., 2011; Jaworski and Proctor, 2000), to inhibit death of hippocampal stem cells (Antonawich and Said, 2002) and to favor survival of sympathetic neuroblasts (Pincus et al., 1994). These data suggest that VIP might be implicated in neurogenesis. However, there is no report regarding the possible effect of VIP on neurogenesis following cerebral ischemia.

Neural stem/progenitor cells within the adult brain germinal centers reside in a neurovascular niche (Li et al., 2011; Ohab et al., 2006; Wang et al., 2007), a microenvironment in which neurogenesis occurs concomitant with angiogenic response to stroke, and is correlated with improvements in behavioral deficits and cognitive function (Thored et al. 2006). In the recent study, we documented that exogenously added VIP promotes angiogenesis by increasing VEGF expression and secretion (Yang et al., 2009, 2013), and decreases cerebral infarct size by inhibiting apoptosis and S100B expression (Yang et al., 2011) in ischemic region after MCAO in rat. The present study was to investigate the effects of VIP treatment on neurogenesis and neurological function during cerebral ischemia. Furthermore, the potential role of VIP on interaction between post-ischemic neurogenesis and angiogenesis was also examined.

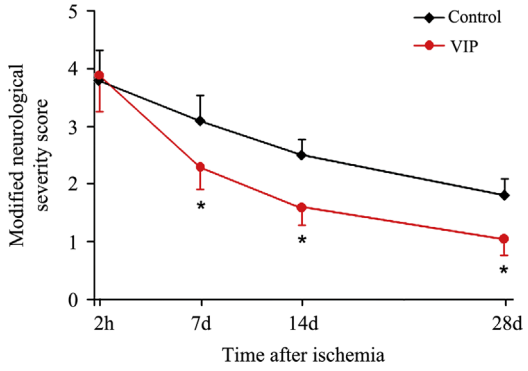

Fig. 1 – Effects of VIP on neurological function after MCAO. Neurological recovery was assessed using a modified neurological severity score at 2 h, 7, 14 and 28 days after MCAO. A higher neurological grade denotes the poorer function. Treatment of VIP improves neurological recovery at 7–28 days after MCAO. *$P<0.05$ compared with control on same day.

2. Results

2.1. VIP improves neurological outcome

Neurologic deficits were measured at predetermined time points after MCAO with the neurological severity score (Fig. 1). Similar neurological impairments were detected at 2 h after onset of ischemia in all animals. A more pronounced decrease in the neurological severity score was observed at 7 days after MCAO in VIP-treated animals, compared with those of the control group. The difference continued to increase with time until the end of the study (28 days after MCAO), indicating that VIP was effective to improve neurological function after cerebral ischemia.

2.2. VIP reduces the infarct volumes

Hematoxylin and eosin staining showed that the infarct was located mainly in the lateral striatum and the surrounding cortical areas (Fig. 2A). Treatment with VIP significantly ($P<0.05$) reduced the infarct volumes at 7, 14 and 28 days after MCAO, compared to control rats (Fig. 2B), implying a neuroprotective effect for exogenous VIP.

2.3. VIP enhances neurogenesis in the ischemic hemispheres

To examine whether administration of VIP enhanced endogenous neurogenesis, rats were given BrdU on 1–6 days after