Neuropharmacology xxx (2015) 1–10

Contents lists available at ScienceDirect

Neuropharmacology

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

The effect of *trans*-resveratrol on post-stroke depression via regulation of hypothalamus–pituitary–adrenal axis

Cong Pang [a, 1], Liang Cao [a, 1], Fan Wu [b, 1], Li Wang [c], Gang Wang [d], Yingcong Yu [e], Meixi Zhang [f], Lichao Chen [f], Weijie Wang [a], Ling Chen [d], Jiejin Zhu [d], Jianchun Pan [b], Hanting Zhang [g], Ying Xu [b, h, **], Lianshu Ding [a, *]

[a] Department of Neurosurgery, Huai'an First People's Hospital, Nanjing Medical University, Huai'an, Jiangsu Province, 223300, China
[b] Brain Institute, School of Pharmacy, Wenzhou Medical University, Wenzhou, Zhejiang Province, 325021, China
[c] Clinical Laboratory, Xuzhou No.1 People's Hospital, Xuzhou, Jiangsu Province, 221002, China
[d] Department of Pharmacy, Hangzhou First People's Hospital, Hangzhou, Nanjing Medical University Affiliated Hangzhou Hospital, Zhejiang Province, 310006, China
[e] Wenzhou Third People's Hospital, Wenzhou Medical University, Wenzhou, Zhejiang Province, 325000, China
[f] Pingyang Hospital of Traditional Chinese Medicine, Pingyang, Zhejiang Province, 325400, China
[g] Department of Behavioral Medicine & Psychiatry, West Virginia University, Morgantown, WV, 26505, USA
[h] Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, State University of New York at Buffalo, Buffalo, NY, 14214, USA

ARTICLE INFO

Article history:
Received 21 January 2015
Received in revised form
15 April 2015
Accepted 18 April 2015
Available online xxx

Keywords:
Trans-resveratrol
Post-stroke depression (PSD)
Middle cerebral artery occlusion (MCAO)
Hypothalamus–pituitary–adrenal axis
BDNF

ABSTRACT

Post-stroke depression (PSD) occurs about 40% among all stroke survivors, but the effective pharmacotherapy is inadequately understood. The present study investigated the effects of a natural polyphenol *trans*-resveratrol (RES) on behavioral changes after middle cerebral artery occlusion (MCAO) and examined what its molecular targets may be. RES was shown to decrease the infarct size and neurological scores after MCAO, suggesting the amelioration of brain damage and motor activity. RES also reversed the depressive-like behaviors 13 days after MCAO, both in the forced swimming and sucrose consumption tests. Moreover, MCAO-induced series abnormalities related to depressive-like behaviors, such as an abnormal adrenal gland weight to body weight ratio, an increased expression of the corticotropin-releasing factor (CRF) in the frontal cortex, hippocampus and hypothalamus, the differential expression of glucocorticoid receptor (GR) in these three brain regions, and a decreased brain-derived neurotrophic factor (BDNF) level, were ameliorated after treatment with increasing doses of RES at 10, 20 and 40 mg/kg via gavage. These findings provide compelling evidence that RES protects the brain against focal cerebral ischemia-induced injury, but most of all is its antidepressant-like effect on PSD, which might at least in part be mediated by regulation of hypothalamus–pituitary–adrenal axis function.

1. Introduction

As the most frequent and important neuropsychiatric consequence of stroke, post-stroke depression (PSD) is estimated to occur about 40% among all stroke survivors (Hackett and Pickles, 2014; Loubinoux et al., 2012; Deplanque et al., 2011). Patients with PSD may develop cognitive impairment, mental regression, depression, discouragement or anxiety compared with stroke patients without depression (Robinson, 2003). The Medicare often underestimates these mental disorders and the treatment for depression after stroke can only be taken care of with little effort or even be ignored (Jeong et al., 2014; Bantsiele et al., 2009), leading to the increases in their physical disability and even mortality. The hypotheses on the pathophysiological nature of PSD have been addressed, i.e. biogenic amine neurotransmitters and neuroendocrine disruption, oxidative stress, as well as neuronal apoptosis (Ji et al., 2014; Wang et al., 2009). More recent evidence

* Corresponding author. Tel.: +86 517 84952317.
** Corresponding author. Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, State University of New York at Buffalo, Buffalo, NY, 14214, USA. Tel.: +1 716 829 5116.
E-mail addresses: yxu9@buffalo.edu (Y. Xu), dlshu@163.com (L. Ding).
[1] Authors contributed equally to this work.

http://dx.doi.org/10.1016/j.neuropharm.2015.04.017
0028-3908/

indicates that improving encephalic condition of ischemia is associated with the amelioration of depression and anxiety (Nabavi et al., 2014). However, the specific etiology and pathophysiology of PSD remain much debate and effective pharmacotherapy for PSD is largely under developed.

Our previous study suggested that polyphenols play important roles in stress-induced depressive-like behaviors due to their regulation of monoaminergic system and hypothalamus–pituitary–adrenal (HPA) axis function, leading to neuroprotection and neurogenesis (Xu et al., 2006, 2007, 2011). Increasing clinical observations suggest that some traumatic brain injuries including middle cerebral artery occlusion (MCAO), may act as precipitating factors in the onset of affective illness of PSD that are closely associated with attenuated HPA axis feedback and decreased neurotrophic protein expression (Oquendo et al., 2003; Weidenfeld et al., 2011). As one of the polyphenols, *trans*-resveratrol (3,4′,5-trihydroxy-trans-stilbene, RES) is the major active component of polygonum cuspidatum, which is also enriched in the grapes, red wine and some other dietary products (Bai et al., 2010). *Trans*-resveratrol has achieved widespread attention for its potential use as a therapeutic agent in the prevention and treatment of numerous diseases, including antioxidant, anti-inflammatory, neuroprotective properties and amelioration of learning and memory impairment (Tredici et al., 1999; Chen et al., 2007; Ranney and Petro, 2009). The previous studies in our laboratory suggested that acute treatment with *trans*-resveratrol exhibits antidepressant-like effect; the underlying mechanism may be involved in the regulation of neurotransmitters dysfunction induced by chronic stress (Yu et al., 2013). However, studies examining the relationship between the neuroendocrine disruptions induced by MCAO and those of polyphenols treatment are lacking.

In the first set of our study, we examined the effects of *trans*-resveratrol on the neurological scores and brain infarct volume after treatment with *trans*-resveratrol for 7 days prior to the MCAO surgery (i.e. 22 h after MCAO). Subsequently, the antidepressant-like effects of *trans*-resveratrol on PSD were observed both 22 h and 14 days after MCAO surgery, in the forced swimming and sucrose preference tests. The related neuroendocrine and neuroprotective parameters, such as adrenal glands index, corticotropin-releasing factor (CRF), glucocorticoid receptor (GR) and brain derived neurotrophic factor (BDNF) expression, were also measured for uncovering the possible mechanism of *trans*-resveratrol treatment on PSD.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley (SD) rats (250–280 g) were obtained from the Animal Center of Shanghai Branch, Chinese Academy of Sciences. Upon arrival, two rats were housed in each cage and acclimatized to a colony room with controlled ambient temperature (22 ± 1 °C), humidity (50 ± 10%) and a 12-h natural light/dark cycle. They were allowed to acclimatize to the colony for 5 days before any experiment. In behavioral tests, rats in every group were intermixed during the observation (10:00 h and 14:00 h) and the observers were unaware of the treatment conditions. All experiments were conducted in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985), as approved by the Nanjing Medical University and Wenzhou Medical University Committee on Animal Care and Use.

2.2. Drugs

Trans-resveratrol and imipramine hydrochloride (IMI) were purchased from Sigma Chemical Co. (USA). Sodium carboxymethyl cellulose was provided by the Beijing Institute of Pharmacology and Toxicology (China). For oral administration (via gavage, i.g.), *trans*-resveratrol was dissolved in 0.5% sodium carboxymethyl cellulose. For intraperitoneal injection, imipramine was dissolved in redistilled water.

3. Experimental design

3.1. Experiment 1#

Ninety-six rats totally were divided into six groups for two sets of study (16 rats/group for experiment 1# and 2#, 6 groups). In this experiment 1# (Fig. 1A), forty-eight rats were divided into six groups (n = 8 for each group, 6 groups) randomly: “Sham” (without MCAO and vehicle treated only); “MCAO” (2 h occlusion followed by 22 h reperfusion and vehicle treated); “MCAO + RES” (with MCAO and 10, 20, 40 mg/kg *trans*-resveratrol treated). “MCAO + IMI” (with MCAO and 10 mg/kg imipramine treated). *Trans*-resveratrol, imipramine or equal volumes of vehicle were given for 7 consecutive days before MCAO surgery. On day 7, rats were subjected to MCAO 30 min before resveratrol treatment. On day 8, 30 min after RES, Vehicle or IMI treatment (22 h after occlusion), the rats were assessed for depressive-like behaviors (sucrose preference test), neurological scores and then sacrificed for examining cerebral infarct volume.

3.2. Experiment 2#

Another 48 rats (n = 8 for each group, six groups) were treated as the same method as the experiment 1#. On day 7, rats were subjected to MCAO. RES, imipramine or equal volumes of vehicle were given once per day for 7 days prior to the MCAO surgery, and continued to give up to 21 days. On day 20th, the neurological scores and the sucrose preference tests were measured. On day 21st, the rats were assessed for forced swimming and locomotor activity tests before they were sacrificed (Fig. 1B). All the tests were taken 30 min after drug treatment. The adrenal glands and brain tissues, such as the frontal cortex, hippocampus and hypothalamus, were separated.

4. Surgery

Focal cerebral ischemia was produced by MCAO procedure as described by Longa et al. (1989) with minor modifications (Longa et al., 1989). Rats were food deprived for approximately 16 h prior to unilateral transient intraluminal right MCAO according to standard procedures. Rats were anesthetized with an appropriate anesthetic (Ryan et al., 2006). Body temperature of the rat was maintained at 36.5 °C ± 0.5 °C during surgery with a heating plate. The fur was surrounded with an appropriate agent (e.g. 70% ethyl alcohol) and the skin was disinfected. To perform transient brain ischemia, a midline neck incision was made and the soft tissues were pulled apart. The right common carotid artery (LCCA) was dissected being free from the surrounding nerves (without harming the vagal nerve) carefully and a ligature was made using 6.0 strings. The external carotid artery (LECA) was then separated and a second knot was made. The right internal carotid artery (LICA) was clipped using a micro vascular clip. Then came the crucial step: cut a small hole in LECA before it bifurcated to the LCCA and the LICA, and a monofilament (0.26 mm in diameter) (Beijing Sunbio Biotech Co. Ltd., Beijing, China) was then introduced into the LICA, until it stopped at the clip. Close the LECA with the third knot to fix the filament in position and open the clipped artery. If the reperfusion is intended, the time of occlusion can vary from 15 to 120 min. In our experiment, rats stayed for 120 min occlusion in a heated cage. Meanwhile, the wound could be closed with a small suture clip. Afterwards the knot on the LCCA was opened and the filament withdrawn. For the final step, the skin was sutured and the rat was kept in a heated cage for 2 h to control its body temperature (Engel et al., 2011).

Please cite this article in press as: Pang, C., et al., The effect of *trans*-resveratrol on post-stroke depression via regulation of hypothalamus–pituitary–adrenal axis, Neuropharmacology (2015), http://dx.doi.org/10.1016/j.neuropharm.2015.04.017