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Effect of Rhizoma Corydalis on focal cerebral infarct in ischemia-reperfusion injured rats

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KEY WORDS Rhizoma Corydalis; reperfusion injury; cerebral infarction

ABSTRACT

AIM: To investigate the effect of Rhizoma Corydalis (RC) on focal cerebral infarct. **METHODS**: A total of 30 Sprague-Dawley (SD) rats were studied. Focal cerebral infarct was established by occluding the bilateral common carotid arteries and the right middle cerebral artery for 90 min. After 24 h reperfusion, the neurological status was evaluated and then the rats were killed and the brain tissue was stained with 2, 3, 5-triphenyltetrazolium chloride. The neurological status and the changes in the area of cerebral infarct were used as an index to evaluate the effect of RC on cerebral infarct. In addition, the whole blood was examined 24 h after RC treatment in the other 24 SD rats. **RESULTS**: Pretreatment with RC 100 mg/kg can improve neurological status and also can reduce the area of cerebral infarct in ischemia-reperfusion injured rats. The counts of erythrocyte and the amount of hematocrit increased in whole blood of RC-treated rats. **CONCLUSION**: RC can improve neurological status and reduce the area of cerebral infarct in ischemia-reperfusion injured rats.

INTRODUCTION

In traditional Chinese medicine, the method of quickening blood and dispelling stasis is used to treat cerebrovascular accident (CVA) and ischemic heart disease because the main etiology of these diseases are considered closely related to blood stasis[1]. Rhizoma Corydalis (RC) is a Chinese herb, which considered having the action of quickening blood, dispelling stasis, and moving the Qi. Therefore, it is frequently used to treat the related disorders of Qi stagnation and the blood stasis, such as dysmenorrhea[2,3]. Several studies find that the components of RC, such as protopine has an inhibitory activity on platelet aggregation[4], and *dl*-tetrahydropalmatine has neuroprotective effect in heatstroke rats[5] and also inhibits calcium anion into cell to prevent neuronal death in ischemia-reperfusion rats[6].

In our laboratory, the animal model of focal cerebral infarct has been established by occluding the bilateral common carotid arteries and right middle cerebral artery for 90 min, and then reperfusing for 24 h (unpublished data). It has been reported that the severity of neurological deficit has a close relationship with the size of the cerebral infarct area in rats with middle cerebral occlusion, and the neurological status may be evaluated by using a grading scale[7]. In addition, cerebral infarct size may be calculated with 2,3,5-triphenyl-tetrazolium chloride (TTC) staining[8,9]. The aim of the present study was to determine the effect of RC on focal cerebral infarct.

MATERIALS AND METHODS

Extraction of RC Extraction of RC was made in the Koda Pharmaceutical Com Ltd (Taoyuan, Taiwan, China). The RC was collected crudely from China, and authenticated by the high performance liquid chromatography (HPLC) system (Hitachi Instruments Service Co, Ltd, Interface D-700, Pump L-7100, UV-Vis Detector L-7420, Ibaraki-Ken, Japan) using Corydalis (Sigma-Aldrich Co Ltd, USA) as a standard. Crude RC 300 g was extracted 1 h using 3 L water. The extracts were filtered, and then was made to plaster colloid and stored in an icebox. The total yield was 39.07 g (13.02 %)

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of RC.

Animals Adult male Sprague-Dawley (SD) rats, weighing 350 – 400 g, were housed in iron cages and maintained on a 12 h light-dark cycle at 25 ℃. All animal experiments were under-taken in accordance to the Guidelines Principles for the Care and Use of Laboratory Animals.

Establishment of an animal model A total of 30 SD rats was studied. The rats were anesthetized with an intraperitoneal injection (ip) of chloral hydrate (400 mg/kg, 1 mL). The rat's blood pressure and heart rate were monitored by a heart rate-blood pressure measuring apparatus (LE 5001 pressure meter, Panlab SLL, Barcelona, Spain), and body temperature was monitored and maintained at (37.0 ± 0.5) ℃ with a heating pad throughout the experimental procedure. The experimental procedure was divided into two steps. First, the rats were placed in a supine position and the bilateral common carotid arteries were exposed through a midline incision in the neck. Then the arteries wrapped with a loop of plastic line (0.1 mm in diameter) and a PE-50 tube (0.2 mm in diameter), respectively. Second, the head of each rat was fixed in a stereotactic apparatus in a prone position. The scalp was incised to create a wound (1.5 cm in length) from the midpoint of the binaural line, then a bone window 3.5 mm in diameter was made after the temporal muscles were separated and the temporal bone was exposed. The olfactory tract and right middle artery were thus clearly visible. Using a nylon line (8 – 0) placed through a surgical needle, a loose tie was made that was then placed on the right middle cerebral artery just in the upper margin of the olfactory tract. The markers for laser Doppler perfusion were monitored (DRT4, Moor Instruments Inc, Wilmington, USA) down from 900 to 200 when the blood flow of the bilateral common carotid arteries were blocked by drawing the loops of plastic line. Then the markers of laser Doppler perfusion were monitored down from 200 to 50 when the blood flow of the right middle cerebral artery were blocked by drawing the loose tie of nylon line. After the blood flow of the bilateral common carotid arteries and right middle cerebral artery was blocked for 90 min, the blood flow was reestablished.

The rats were randomly divided into 5 groups ($n = 6$ rats) as following: A) Sham group, the bilateral common carotid arteries and the right middle cerebral artery were exposed, but the blood flow was not blocked; B) Control group, the blood flow of the bilateral common carotid arteries and the right middle cerebral artery was blocked for 90 min followed by reperfusion for 24 h; C) RC100 group, the methods of blood flow blocking were identical to the control group, but RC (100 mg/kg, ip, in 1 mL PBS solution) was administered 30 min prior to blocking the blood flow; D) RC50 group, the methods were identical to the RC100 group, but using RC 50 mg/kg in 1 mL PBS solution; E) PBS group, the methods were identical to the RC100 group, but 1.0 mL PBS solution was administrated 30 min prior to blocking the blood flow.

The other 24 SD rats were randomly divided into four group ($n = 6$) as following: 1) Normal group, no any drugs were given; 2) RC100 group, ip injection of RC 100 mg/kg; 3) RC50 group, ip injection of RC 50 mg/kg; 4) PBS group, ip injection of PBS solution 1.0 mL/kg 24 h after drug administration. The rats were under anesthesia with chloral hydrate (400 mg/kg, 1 mL, ip), and the whole blood samples of 3.0 mL were obtained by transcardiac puncture. The whole blood was used to measure the counts of erythrocyte, leucocyte, and platelet and the amount of hematocrit and hemoglobin.

Evaluation of neurological status The neurological status of each rat was evaluated carefully according to neurological examination grading system[7]. A grading scale of 0 – 3 was used to estimate neurological status of the rats. Briefly, the tail of the rats was caught gently, and the rats were suspended in the air one meter above the floor, and then observed for forelimb flexion. Grade 0: No neurological deficit was found and the rats extended both forelimbs toward the floor; Grade 1: The rats with forelimb flexion and no other neurological deficit was observed; Grade 2: The rats were placed on the upper surface of a iron cage and grasped firmly by their claws with the tail caught by hand, and then gentle lateral pressure was applied from the rats shoulder. The rat's decreased resistance to lateral push toward the paretic limb; Grade 3: The same neurological status as Grade 2, and circling behavior was observed during the rats move about freely.

Measurement of infarct size After evaluation of neurological status, the brains of the rats were removed after transcardiac perfusion of 0.9 % NaCl and 4 % Paraformaldehyde under anesthesia with chloral hydrate (400 mg/kg, 1.0 mL, ip). The brain of each rat was sectioned coronals into 2 mm thickness pieces using a plastic model of the rat brain. The samples were then placed in 2 % TTC solution in a 37 ℃ room for 15 min allowing the white cerebral infarct area and the red-purple normal brain tissue area to be differentiated clearly.

Finally the samples were fixed by 10 % formalin solution.

The areas of the cerebral infarct of the first six pieces from frontal tip were measured using an image-analysis system (Image-Pro Lito Version 3.0, Media Cybernetics, USA). The ratio of infarct area and total brain area in each piece of rat brain was calculated, and the data were represented as a percentage (%).

Laboratory examination The counts of erythrocyte, leucocyte, and platelet, and the amount of hematocrit and hemoglobin of the whole blood measured by a Micro cell counter (Sysmex, Micro cell counter F-800, Japan).

Statistical analysis The data are represented as $x \pm s$. One-way analysis of variance (ANOVA) followed by Scheffe's test was used for comparisons among groups. $P < 0.05$ was considered statistically significant.

RESULTS

The blood flow of the bilateral common carotid arteries and the right middle cerebral artery was blocked for 90 min in the 24 SD rats. We found that all of the rats developed cerebral infarct 24 h after reperfusion. After TTC staining, the infarct area of the rat brain was a white color, whereas the non-infarct area was a red-purple color. Pretreatment with Rhizoma Corydalis 100 mg/kg (RC100) and 50 mg/kg (RC50) resulted in a lower ratio of the infarct area than the control group without treatment (Cont) or the PBS group with PBS treatment. No infarct was noted in the Sham group (Fig 1).

Effect of RC on neurological status in ischemia-reperfusion injured rats The neurological deficit was observed in the side contralateral to the cerebral infarct side in the ischemia-reperfusion injured rats, included left forelimb flexion, decrease of resistance during lateral push toward the paretic side, and circling behavior developed during the rats move about freely.

Intraperitoneal administration of RC 100 mg/kg can improve neurological status in ischemia-reperfusion injured rats ($P < 0.05$, Fig 2), but no similar effect was observed in the RC 50 mg/kg ($P > 0.05$, Fig 2).

Effect of RC on cerebral infarct size in ischemia-reperfusion injured rat The ratio of cerebral infarct area in the RC100 group with 5.1 % ± 1.4 % and the RC50 group with 6.8 % ± 1.3 % were lower than that of the control group with 10.5 % ± 2.1 % and PBS group with 9.1 % ± 2.7 % ($P < 0.05$, Fig 1, 3). There are similar ratio of cerebral infarct between the control group and the PBS group ($P > 0.05$, Fig 1, 3).

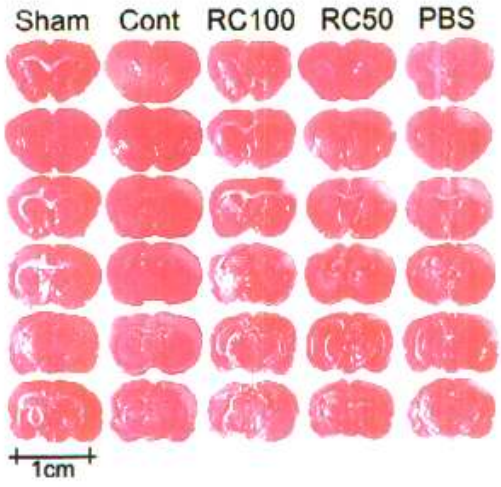

Fig 1. Focal cerebral infarct developed after the blood flow of bilateral common carotid arteries and right middle cerebral artery was blocked for 90 min followed by 24 h reperfusion in Sprague-Dawley rats. On 2,3,5-triphenyl-tetrazolium chlorides staining the infarct area of the rat brain showed white color, whereas non-infarct area was red-purple color. Sham: sham group for which blood flow of the bilateral common carotid arteries and the right middle cerebral artery was not blocked; Cont: control group for which the blood flow of the bilateral common carotid arteries and the right middle cerebral artery were blocked for 90 min followed by 24 h reperfusion, and no drug treatment; RC100: RC100 group rats underwent the same procedures as the control group, but with RC 100 mg/kg pretreatment; RC50: RC50 group rats underwent the same procedures as in the RC100 group, with RC 50 mg/kg pretreatment; PBS: PBS group, rats received the same procedures as RC100 group rats, with PBS pretreatment.

Effect of RC on whole blood in ischemia-reperfusion injured rats The count of erythrocyte of the whole blood in RC100 group was more than that in normal group and in PBS group ($P < 0.01$, Tab 1), and the amount of hematocrit of whole blood in RC100 group was more than that of normal group ($P < 0.05$, Tab 1), but the counts of leucocyte and platelet and hemoglobin amount of the whole blood indicated no changes 24 h after treatment of RC 100 mg/kg or RC 50 mg/kg in rats ($P > 0.05$, Tab 1)

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Tab 1. Effect of Rhizoma Corydalis on whole blood in ischemia-reperfusion rats. $n = 6$. $\bar{x} \pm s$. $^bP < 0.05$, $^cP < 0.01$ *vs* Normal. $^eP < 0.05$ *vs* PBS.

Group	$10^{-12} \times$ RBC/L^{-1}	Hb (mg/L)	Hct (%)	$10^{-9} \times$ WBC/L^{-1}	$10^{-10} \times$ Platelet/L^{-1}
Normal	9.7±0.8	171±14	55±4	10±7	10.7±2.1
PBS	10.2±1.1	162±7	59±6	10±6	12.3±3.0
RC50	10.8±0.7	165±5	63±4	9±6	12.7±2.0
RC100	12.1±1.4^{ce}	167±13	69±11^b	6.0±2.3	13.3±1.7

Normal: rats without any drug treatment; PBS: rats with PBS solution treatment (1 mL/kg); RC50: rats with Rhizoma Corydalis 50 mg/kg treatment; RC100: rats with Rhizoma Corydalis 100 mg/kg treatment; RBC: Erythrocyte; Hb: Hemoglobin; Hct: Hematocrit; WBC: Leucocyte.

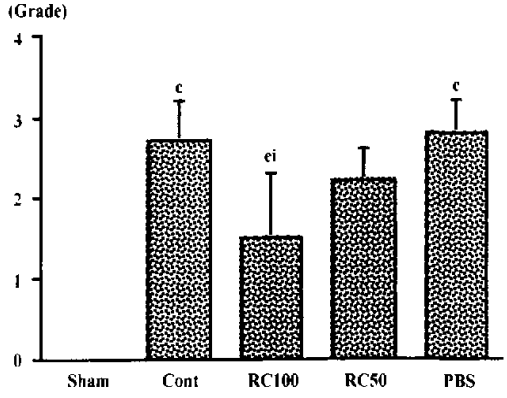

Fig 2. Effect of Rhizoma Corydalis on neurological deficit in ischemia-reperfusion injured rats. Grade: grading scale of neurological status. $n = 6$. $\bar{x} \pm s$. $^cP < 0.01$ *vs* Sham. $^eP < 0.05$ *vs* Cont. $^iP < 0.01$ *vs* PBS.

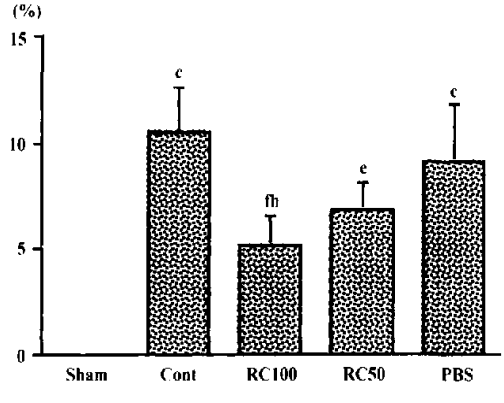

Fig 3. Effect of Rhizoma Corydalis on cerebral infarct in ischemia-reperfusion injured rat. Pretreatment with Rhizoma Corydalis (RC) 100 mg/kg or 50 mg/kg reduced the area of cerebral infarct. $n = 6$. $\bar{x} \pm s$. $^cP < 0.01$ *vs* Sham. $^eP < 0.05$, $^fP < 0.01$ *vs* Cont. $^bP < 0.05$ *vs* PBS.

DISCUSSION

In the present study, the blood flow of the bilateral common carotid arteries and the right middle cerebral artery was blocked for 90 min and reperfusion of 24 h. The rats developed cerebral infarct, and this animal model was similar to cerebral infarct in humans, and also similar to the reports of several studies[7,10]. The neurological deficits in rats with cerebral infarct were observed including left forelimb flexion, decrease of resistance when the rat was pushed laterally toward the left paretic side, and ambulation in a circle toward the left paretic limb, these behaviors also were similar to previous report[1].

Our results indicated that RC (100 mg/kg, ip) 30 min prior to blocking blood flow can reduce neurological deficits and also can decrease the ratio of cerebral infarct area in ischemia-reperfusion injured rats, suggesting that RC may be useful in the treatment of cerebral infarct in humans. Speroxide anion generates during the period of reperfusion after cerebral ischemia[11], and free radical including superoxide and hydroxyl radicals is involved in the cerebral damage induced by ischemia-reperfusion tissue injury[12~14]. The generation of free radicals plays an important role in triggering the ischemic neuronal damages causing delayed neuronal death[15]. In addition, the activity of superoxide dismutase as a major superoxide anion scavenging system decrease in patients with acute cerebral infarct[16] and in acute stage of cerebral infarct in rats[17]. Ischemia-reperfusion in cerebral ischemia and myocardial infarct causes the disruption of calcium homeostasis and results in influx of calcium into the ischemic cells. This high concentration of intracellular calcium may produce mitochondria abnormalities and eventually render the irreversible cell death[12,18]. Several studies find that *dl*-tetrahydro-

palmatibe as a component of RC may improve brain edema and the activities of electroencephalogram in focal cerebral ischemia-reperfusion rats, and this action results from its calcium influx inhibition[6]. In addition, *dl*-tetrahydropalmatibe has an action of calcium influx inhibition in isolated rat heart[19]. Dehydrating hyperosmolar agents such as mannitol or glycerol have been prescribed to reduce brain edema, and calcium channel blocking agent such as nimodipine may reduce neurological deficit produced by cerebral ischemia[20]. Our results indicated that RC 100 mg/kg may increase the counts of erythrocyte and the amount of hematocrit, we assumed that these effect of RC as like, as the action of dehydrating hyperosmolar agents, at least in part, may explain the results of the present study.

In conclusion, the results of this study demonstrate that RC can improve neurological status and reduce the area of cerebral infarct in ischemia-reperfusion injured rats, suggesting it may be useful in the treatment of cerebral infarct in humans. We assumed that this effect of RC partly results from as like, as the action of dehydrating hyperosmolar agent, but further study is needed.

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延胡索对缺血再灌注损伤大鼠局灶性脑梗死的作用

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关键词 延胡索; 再灌注损伤; 脑梗死

目的:探讨延胡索对局灶性脑梗死的作用. **方法**:

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总共有 30 只 Sprague-Dawley (SD)大鼠被用来研究. 局灶性脑梗死动物模型的建立是将两侧的颈总动脉和右侧的中大脑动脉的血流阻断 90 min 后, 再经 24 h的灌流, 然后评估它们的神经状态. 大鼠被牺牲取脑, 并作成切片用 2,3,5-triphenyl-tetrazolium chloride 染色. 以神经的状态和脑梗死面积的变化作为指标来评估延胡索对脑梗死的作用. 另外, 24 只 SD 大鼠腹腔注射延胡索, 经 24 h 后从心脏采血测量血液的变化. **结果**: 延胡索 100 mg/kg 腹腔注射能够改善大鼠神经缺损的症状和减少脑梗死的面积以及能增加全血中红血球的数目和提高血比容 (hematocrit). **结论**: 延胡索在缺血再灌流损伤大鼠能改善神经状态和减少脑梗死面积.

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《中国药理学报》2000 年度十佳优秀论文评选揭晓

经本刊国内 21 位编委专家投票评选, 在 2000 年本刊发表的论文中选出"《中国药理学报》2000 年度十佳优秀论文". 现将评选结果公布如下(按得票数多少排列顺序), 予以表彰. 欢迎广大读者点评, 欢迎继续踊跃投稿.

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