Effects of rhynchophylline on monoamine transmitter contents of striatum and hippocampus in cerebral ischemic rats

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Abstract: AIM To explore the protection mechanism of rhynchophylline (Rhy) on cerebral ischemic injury. **METHODS** The cerebral ischemic injury of rats was induced by middle cerebral artery occlusion. The extracellular fluid of striatum and hippocampus in cerebral ischemic rats was collected by using microdialytic approach at 30, 60, 90 and 120 min, respectively. Then norepinephrine (NE), 5-hydroxyindoleacetic acid (5-HIAA), 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were measured with reverse phase high performance liquid chromatograph-electrochemical detector. **RESULTS** Cerebral ischemic induced decreases in extracellular 5-HIAA, DOPAC and HVA in striatum and hippocampus, but NE was increased. Rhy inverses the changes in 5-HIAA, DOPAC, HVA and NE in cerebral ischemic rats. **CONCLUSION** Rhy can regulate release and metabolism of the intracerebral monoamine transmitters in striatum and hippocampus of cerebral ischemic rats.

Key words: rhynchophylline; cerebral ischemia; norepinephrine; hydroxyindoleacetic acid; 3, 4-dihydroxyphenylacetic acid; homovanillic acid; chromatography, high performance liquid; microdialysis

CLC number: R971
Document code: A
Article ID: 1000-3002(2004)04-0253-06

Recent study indicated that 5-hydroxytryptamine (5-HT) could bring about excitotoxicity mediated by receptor of 5-HT_2[1,2]. Magnoni, *et al*[3] reported that the effect of norepinephrine (NE) and epinephrine (E) on contraction of blood vessel could aggravate cerebral ischemia and cerebral edema. Study of Prado, *et al*[4] showed that ischemia activated adenosine cyclase and induced a significant increase in cyclic adenosine monophosphate (cAMP), which aggravated the glutamine excitotoxicity. In ischemic brain tissue, the release of glutamate can increase the release of DA in striatum mediated by *N*-methyl-*D*-aspartate (NMDA) receptors[5]. A large amounts of DA release can not only produce H_2O_2 (hydroperoxide), but also confuse the system of glutathione reductase, simultaneously, which decrease the ability of free radical clearance and results in the accumulation of free radical[6]. In ischemia, glutamate release at a synapse leads to intracellular calcium overload, which activates phospholipase, kinase and endonuclease, results in degradation of the membrane phospholipids, protein and DNA, as a result, the membrane, nerve fiber and the structure of cell are damaged[7]. At the same time, Simantov, *et al*[8] reported that DA could induce apoptosis. Therefore, the metabolism of monoamine transmitter is the important factor in ischemia.

Rhynchophylline (Rhy) is an alkaloid extracted from Chinese herb *Uncaria rhynchophylla* (Miq.) Jackson. Rhy possesses pharmacological effects of hypotension, vascular relaxation and bradycardia[9-11]. It could also protect neurons from damage induced by dopamine, which behaves as a free radical at higher concentration, and inhibits NMDA receptor expression[12,13]. Recently studies showed that Rhy possesses protective effect on cerebral ischemia[14], but its influence on monoamine neurotransmitters is not certain. In present study, we investigate the effects of Rhy on intracerebral monoamine neurotransmitters in cerebral ischemia rats and try to explore the protective

Received date: 2003-09-02 **Accepted date**: 2004-03-22
Foundation item: The project supported by Stadholder Talent Fundation of Guizhou Provine(2001016)
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mechanisms of Rhy on the cerebral ischemic injury.

1 MATERIALS AND METHODS

1.1 Materials and apparatus

Rhy (white crystal, purity > 98%) was provided by Guangxi Institute of Traditional Chinese Medicine and Materia Medica. It was dissolved in hydrochloride 0.1 $mol \cdot L^{-1}$ and diluted with distilled water to pH 6.5 before used. The reagents of NE, homovanillic acid(HVA), 3,4-dihydroxyphenylacetic acid (DOPAC), 5-hydroxyindoleacetic acid(5-HIAA), 3,4-dihydroxybenzylamine(DHBA) were purchased from Sigma Chemical Company.

High performance liquid chromatograph (HPLC) with reverse phase column (C_{-18}, 25 cm × 4.6 mm, 5 μm, Shimadzu Co.), WZS-50F microinjection pump(Medical Instrument Factory, Zhejiang University), stereotaxic apparatus for rat brain(Jiangwan-Ⅱ, The Second Precision Instrument Factory, Shanghai), dialysis membrane (50 000 Daltons cut-off, provided by CMA, Stockholm, Sweden); nylon line (d = 0.28 mm, Eka Chemicals AB, Bohus, Sweden), were used respectively.

1.2 Treatment of animals

Adult Wistar rats of both sexes, weighing 280 – 320 g, were used in experimens (purchased from Experimental Animal Center of Daping Hospital, the Third Military Medical University, Grade Ⅱ, Certificate No. 2001015). The rats were divided into 6 groups at random: sham-operated group, cerebral ischemic group, Rhy Ⅰ group (5 $mg \cdot kg^{-1}$), Rhy Ⅱ group (10 $mg \cdot kg^{-1}$), Rhy Ⅲ group (15 $mg \cdot kg^{-1}$), control group (nimodipine, Nim, 0.125 $mg \cdot kg^{-1}$), and each group included 10 rats.

1.3 Rat model of middle cerebral artery occlusion

All rats were fixed in stereotaxic apparatus under 35% chloral hydrate anesthesia, one side common carotid artery, external carotid artery and internal carotid artery were separated, and the external carotid artery as well as its branches were deligated and cut off from distal tip. The Ala-palatine artery (the branch of internal carotid artery) was deligated. A nylon line (d = 0.28 mm) glued silicage oil was inserted to the stump of external carotid artery and along with the cross-linking of common carotid artery and external carotid artery, drived softly towards internal carotid artery to the cross of internal carotid artery of intracranium, and at last the blood flow of middle cerebral artery was blocked. In sham-operated group, nylon line inserted from stump of external carotid artery but not to the intracranium's internal carotid artery.

1.4 Microdialysis

Rats were placed in stereotaxic apparatus under 35% chloral hydrate anesthesia, an incision was made in the skin of head, to exposure skull, one hole was drilled on the right side of the skull which was 0.3 mm in front of bregma and 3.0 mm lateral to the midline with dental driller. The dialysis probe (50 000 Daltons cut-off, membrane's length was 2 mm) was implanted through the hole on the striatum, the depth was 3.3 mm below dura. The position was determined according to Pellergrino's Stereotaxic Atlas of the Rat Brain. The dialysis probe was perfused with artificial cerebrospinal fluid (ACSF, compositon in $mmol \cdot L^{-1}$: NaCl 145, KCl 2.7, $CaCl_2$ 1.2, $MgCl_2$ 1.0, Na_2HPO_4 2.0, pH 7.0), flow rate 1.6 $\mu L \cdot min^{-1}$. Before implantation, each probe was flushed through with distilled water for 10 min (flow rate 1.6 $\mu L \cdot min^{-1}$) and examined microscopically to ensure that there were no leaks. The completed fiber was then unilaterally implanted in the striatum 30 min for equilibrium. All rats except sham-operated group and cerebral ischemic group were injected by drugs from femoral vein. The perfusate (known as dialysate once it has passed through the probe) was collected at 30, 60, 90 and 120 min, respectively. The perfusate 20 μL was injected directly on HPLC.

1.5 High performance liquid chromatograghy analysis

NE, 5-HIAA, DOPAC and HVA in the perfusate were isolated and determined with following

mobile phase: CH_3COONa 30 mmol · L^{-1}, CH_3COOH 0.2 mmol·L^{-1}, SDS 0.3 mmol·L^{-1}, $EDTANa_2$ 0.27 mmol·L^{-1}, NaCl 1.7 mmol·L^{-1} and methanol 15%. The flow rate was 1.0 mL·min^{-1}. The effluent was monitored (Shimadzu electric chemical detector) and the data were recorded and computed[15].

1.6 Histological analysis

The rats were sacrificed after perfusion. The correct position of the probe in the striatum and the nylon line in the cross of internal carotid artery of intracranium were verified in every animal during anatomic assessments. Only animals with the probe and nylon line in the correct position were used for the statistical analysis.

1.7 Statistical analysis

The results were calculated as concentration of monoamine transmitters and their metabolites. Adopt q-test of Microsoft Excel. There is discrepancy when $P < 0.05$ and significant discrepancy when $P < 0.01$.

2 RESULTS

2.1 Effects of rhynchophylline on monoamine transmitters of striatum

As showed in Tab 1, in the cerebral ischemic rats, the extracellular concentrations of 5-HIAA, DOPAC and HVA in striata were decreased, while

Tab 1. Effects of rhynchophylline on 5-HIAA, DOPAC, HVA and NE in striatum of cerebral ischemic rats

Drug/mg·kg^{-1}	Concentration in perfusate/mg·L^{-1}			
	30	60	90	120(min)
		5-HIAA		
Sham-operated	0.080 ± 0.017	0.077 ± 0.015	0.077 ± 0.018	0.078 ± 0.005
Ischemic	0.049 ± 0.010$^{\#}$	0.053 ± 0.006$^{\#}$	0.053 ± 0.005$^{\#}$	0.051 ± 0.017$^{\#}$
Rhynchophylline 5	0.039 ± 0.007	0.058 ± 0.019	0.056 ± 0.018	0.055 ± 0.015
10	0.076 ± 0.003**	0.075 ± 0.004**	0.073 ± 0.014*	0.070 ± 0.013
15	0.098 ± 0.021**	0.096 ± 0.008**	0.096 ± 0.006**	0.110 ± 0.023**
Nimodipine 0.125	0.053 ± 0.008	0.049 ± 0.026	0.049 ± 0.017	0.076 ± 0.007
		DOPAC		
Sham-operated	3.3 ± 0.4	3.2 ± 0.5	3.3 ± 0.6	3.2 ± 0.5
Ischemic	2.3 ± 0.6$^{\#}$	2.2 ± 0.4$^{\#}$	2.3 ± 0.4$^{\#}$	2.4 ± 0.3$^{\#}$
Rhynchophylline 5	2.3 ± 0.4	2.4 ± 1.0	2.5 ± 0.6	2.6 ± 0.3
10	3.3 ± 0.3**	3.3 ± 0.4*	3.5 ± 0.3**	3.4 ± 0.3**
15	4.4 ± 0.4**	4.4 ± 0.4**	4.6 ± 0.6**	4.3 ± 0.6**
Nimodipine 0.125	2.2 ± 0.6	2.3 ± 0.6	2.6 ± 0.8	2.4 ± 0.5
		HVA		
Sham-operated	0.85 ± 0.08	0.84 ± 0.14	0.98 ± 0.32	0.86 ± 0.20
Ischemic	0.53 ± 0.10$^{\#}$	0.57 ± 0.11$^{\#}$	0.55 ± 0.13$^{\#}$	0.563 ± 0.013$^{\#}$
Rhynchophylline 5	1.00 ± 0.13**	1.10 ± 0.23*	1.21 ± 0.50*	1.10 ± 0.42*
10	1.30 ± 0.29**	1.22 ± 1.97**	1.29 ± 0.34**	1.43 ± 0.28**
15	2.87 ± 1.65*	2.74 ± 1.52*	2.85 ± 1.38**	2.87 ± 0.92*
Nimodipine 0.125	0.47 ± 0.15	0.58 ± 0.24	0.98 ± 0.10**	0.97 ± 0.14**
		NE		
Sham-operated	3.2 ± 0.5	3.1 ± 0.9	2.95 ± 0.29	3.1 ± 0.4
Ischemic	18.2 ± 3.7$^{\#\#}$	12.7 ± 3.3$^{\#\#}$	12.0 ± 2.9$^{\#\#}$	10.6 ± 3.8$^{\#\#}$
Rhynchophylline 5	6.0 ± 1.6**	4.8 ± 1.1**	4.8 ± 1.3**	5.6 ± 1.7*
10	3.6 ± 0.5**	3.3 ± 0.2**	3.2 ± 3.8**	3.2 ± 0.7**
15	2.6 ± 0.6**	2.4 ± 0.7**	2.3 ± 0.6**	2.3 ± 0.7**
Nimodipine 0.125	4.0 ± 2.2**	4.0 ± 1.5**	3.0 ± 1.3**	2.3 ± 0.8**

5-HIAA: 5-hydroxyindoleacetic acid; DOPAC: 3,4-dihydroxyphenylacetic acid; HVA: homovanillic acid; NE: norepinephrine. Ischemia time: 30, 60, 90, 120 min. $\bar{x} \pm s$, $n = 10$. $^{*}P < 0.05$, $^{**}P < 0.01$, compared with ischemic group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, compared with sham-operated group.

NE was increased; Rhy could bring about a simultaneous release of striatal 5-HIAA, DOPAC and HVA in a dose-dependent manner (Rhy 10, 15 mg·kg^{-1}), but decrease level of NE in a dose-dependent manner well.

2.2 Effects of rhynchophylline on monoamine transmitters of hippocampus

In the cerebral ischemic rats, the extracellular concentrations of 5-HIAA, DOPAC and HVA in hippocampus were decreased, while NE was increased; Rhy could bring about a simultaneous release of striatal 5-HIAA and DOPAC in a dose-dependent manner (Rhy 5, 10 mg·kg^{-1}), HVA (Rhy 10, 15 mg·kg^{-1}), but decrease level of NE in a dose-dependent manner (Tab 2).

Tab 2. Effects of rhynchophylline on 5-HIAA, DOPAC, HVA and NE in hippocampus of cerebral ischemic rats

Drug/mg·kg^{-1}	Concentration in perfusate/mg·L^{-1}			
	30	60	90	120(min)
		5-HIAA		
Sham-operated	0.065 ± 0.009	0.065 ± 0.008	0.064 ± 0.015	0.065 ± 0.012
Ischemic	0.049 ± 0.012$^{\#}$	0.049 ± 0.005$^{\#\#}$	0.045 ± 0.007$^{\#}$	0.047 ± 0.010$^{\#}$
Rhynchophylline 5	0.055 ± 0.020	0.064 ± 0.009**	0.065 ± 0.020*	0.069 ± 0.012*
10	0.056 ± 0.013	0.065 ± 0.010**	0.068 ± 0.009**	0.075 ± 0.024*
15	0.124 ± 0.021**	0.11 ± 0.57*	0.13 ± 0.47**	0.14 ± 0.41**
Nimodipine 0.125	0.21 ± 0.79**	0.24 ± 0.94**	0.20 ± 0.60**	0.21 ± 0.10**
		DOPAC		
Sham-operated	2.3 ± 0.3	2.3 ± 0.5	2.3 ± 0.3	2.2 ± 0.9
Ischemic	1.6 ± 0.2$^{\#}$	1.5 ± 0.4$^{\#}$	1.5 ± 0.4$^{\#}$	1.7 ± 0.4$^{\#}$
Rhynchophylline 5	3.4 ± 0.9*	3.7 ± 1.0**	4.6 ± 1.4*	3.7 ± 0.7**
10	5.7 ± 1.7**	5.4 ± 1.4**	5.7 ± 1.4**	5.7 ± 0.9**
15	6.8 ± 2.3**	5.6 ± 1.1**	6.7 ± 0.8**	5.6 ± 1.4**
Nimodipine 0.125	9.6 ± 2.5**	9.7 ± 3.2**	10.0 ± 1.8**	9.1 ± 1.8**
		HVA		
Sham-operated	0.91 ± 0.10	0.94 ± 1.56	0.96 ± 0.19	0.99 ± 0.12
Ischemic	0.44 ± 0.10$^{\#\#}$	0.33 ± 0.10$^{\#\#}$	0.32 ± 0.87$^{\#\#}$	0.33 ± 0.67$^{\#\#}$
Rhynchophylline 5	1.04 ± 0.42*	0.84 ± 0.34*	1.06 ± 0.32**	1.16 ± 0.21**
10	1.50 ± 0.09**	1.47 ± 0.15**	1.5 ± 0.3**	1.52 ± 0.28**
15	1.45 ± 0.62*	1.68 ± 0.65*	1.42 ± 0.63**	1.46 ± 0.52**
Nimodipine 0.125	3.16 ± 0.46**	2.99 ± 0.85**	2.27 ± 0.71**	2.10 ± 1.13*
		NE		
Sham-operated	3.4 ± 0.8	3.4 ± 0.6	3.4 ± 0.8	3.4 ± 0.7
Ischemic	9.5 ± 2.3$^{\#\#}$	9.9 ± 4.4$^{\#\#}$	8.7 ± 2.0$^{\#\#}$	8.6 ± 1.3$^{\#\#}$
Rhynchophylline 5	4.8 ± 3.4**	5.7 ± 3.3*	4.8 ± 3.0**	4.9 ± 1.6**
10	5.1 ± 2.4**	4.9 ± 2.6*	4.5 ± 2.2**	4.5 ± 1.7**
15	1.3 ± 0.6**	2.0 ± 0.8**	1.7 ± 0.6**	1.6 ± 0.5**
Nimodipine 0.125	2.1 ± 0.4**	2.0 ± 0.5**	1.5 ± 0.6**	1.7 ± 0.4**

See Tab 1 for abbreviations. $\bar{x} \pm s$, $n = 10$. $^{*}P < 0.05$, $^{**}P < 0.01$, compared with ischemic group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, compared with sham-operated group.

3 DISCUSSION

It has been reported that accumulation of monoamine transmitters in the intercellular space after ischemia prompted and aggravated brain injury through damaging neuron directly, decreasing regional cerebral blood flow, enhancing excitatory amino acid release, spuring free radical accumulation and inducing apoptosis. Obrenovitch, *et al*[16] reported that the extracellular concentrations of NE, DA and 5-HT increased sharply in striatum of transient ischemic gerbil. Moreover a high level of neurotransmitters was remained after the period of ischemia. The other study showed that the concentrations of DA and 5-HT raised in the extracellular fluid while the concentrations of DOPAC, HVA and 5-HIAA decreased during the cerebral ischemia[17].

Our data indicated that the concentrations of 5-HIAA, HVA and DOPAC were decreased while NE was increased in both hippocampus and striatum of the ischemic rats (Tab 1, 2), which is similar to the document evidences. It is known that ischemia results in Ca^{2+} overloading, which can induce neurotransmitters release and the extracellular level is increased[18]. Moreover, the disturbance of the energy due to ischemia also results in a decrease of the activity of monoamine oxidase and catechol-*O*-methyltransferase. Study of Wang, *et al*[19] indicated that Rhy could block calcium channel. Kai, *et al*[20] reported that Rhy decreased the open time of calcium channel, but increased the open probability of calcium-activated potassium channels in isolated rat pulmonary artery smooth muscle cells. Therefore, it is easy to understand that Rhy reduces NE level, but increases the levels of 5-HIAA, HVA and DOPAC in dose-dependent manner in the cerebral ischemic rats.

Our previous study showed that Rhy possessed a protective effect on cerebral ischemia in rats and hamsters, which was related with the inhibition of nitric oxide synthesis and intracellular calcium overload[14]. It is reported that Rhy inhibited rabbit platelet aggregation induced by arachidonic acid, collagen and ADP, and reduced the thromboxane B_2 generation in PRP induced by collagen[21,22]. Rhy produces protective effect on the cerebral ischemia by the hemorheological amelioration and calcium channel blocking. A higher concentration of monoamine neurotransmitter can induce apoptosis in neurons by free radical action, and extracellular NE can induce local vasoconstriction. Therefore, the present data indicate that the metabolites increase and NE decrease are not only the result but also the mechanism of Rhy on cerebral ischemia. However, the classical calcium blocker Nim mainly affects the metabolite level of the monoamine neurotransmitters in hippocampus. Rhy accelerates the metabolism of monoamine transmitters in both hippocampus and striatum. The difference between Rhy and Nim whether due to Rhy directly affecting the enzymes is remained to be further studied.

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钩藤碱对脑缺血大鼠纹状体及海马单胺类递质含量的影响

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摘要: 目的 探索钩藤碱对大鼠脑缺血损伤的机制。**方法** 采用大鼠大脑中动脉缺血模型,利用微透析方法收集正常及脑缺血后不同时间点纹状体和海马细胞外液(透析液)。经反相高效液相电化学法检测其单胺类神经递质含量的变化。**结果** 大鼠脑缺血后纹状体和海马细胞外液中 5-羟吲哚乙酸(5-HIAA)、3,4-二羟苯酰乙酸(DOPAC)和高香草酸(HVA)含量下降,去甲肾上腺素(NE)含量上升,钩藤碱能升高脑缺血后细胞外液 5-HIAA, DOPAC 和 HVA 的含量,降低 NE 的含量。**结论** 钩藤碱能调节脑缺血大鼠纹状体内和海马单胺类神经递质及代谢物的含量。

关键词: 钩藤碱; 脑缺血; 去甲肾上腺素; 羟基吲哚乙酸; 3,4-二羟苯酰乙酸; 高香草酸; 色谱法, 高效液相; 微透析

基金项目: 贵州省省长人才基金资助课题(2001016)

(本文编辑 石 涛)