ISSN 1671-4083 Acta Pharmacol Sin 中国药理学报 2002 Jul; 23 (7): 591 - 596
http://www.chinaphar.com


# Effects of various principles from Chinese herbal medicine on rhodamine123 accumulation in brain capillary endothelial cells[1]

HE Ling[2], LIU Guo-Qing
(*Department of Pharmacology, China Pharmaceutical University, Nanjing 210009, China*)

**KEY WORDS** P-glycoprotein; blood-brain barrier; multiple drug resistance; xanthenes; isoquinolines

## ABSTRACT

**AIM**: To search for novel effective P-glycoprotein (P-gp) reversal agents in the blood-brain barrier (BBB). **METHODS**: Using rhodamine123 (Rh123) to examine the functional activity of P-gp in cultured bovine brain capillary endothelial cells (BCEC) and screen various principles on P-gp modulation in BBB. **RESULTS**: All of tested compounds (1 - 10 μmol/L) increased the intracellular accumulation of Rh123 in a concentration-dependent manner. The rank order of these agents in increasing Rh123 accumulation in BCEC was: cyclosporin A (CsA) > tetrandrine (Tet) > vincrinstine (VCR) ≈ flunarizine (Flu) > *dl*-tetrahydropalmatine (*dl*-THP) > dauricine (DRC) > azithromycin (Azi) > verapamil (Ver) ≈ berbamine (BBM) > daurisoline (DRS) > berberine (BBR) ≈ doxorubicin (Dox) > *l*-tetrahydropalmatine (*l*-THP) > tetramethylpyrazine (TMP). These agents at concentration of 10 μmol/L increased Rh123 accumulation by 346 %, 203 %, 136 %, 129 %, 115 %, 103 %, 92 %, 87 %, 81 %, 75 %, 67 %, 67 %, 63 %, and 54 %, respectively. The effects of CsA, Tet, Ver, Flu, Azi, and *dl*-THP on cellular accumulation of Rh123 in BCEC were reversible. When CsA, Tet, Ver, Flu, Azi, or *dl*-THP-pretreated BCEC were examined at 48, 36, 24, 36, 36, or 12 h, respectively, after removing the agent, the amount of cellular Rh123 accumulation in BCEC returned to control levels (no drug treatment). **CONCLUSION**: The functional activity of P-gp on the blood-brain barrier could be modulated by various MDR-reversing agents and some principles with low toxicity extracted from medicinal herbs, such as some isoquinoline alkaloids without permanent modifying effects on the intrinsic level of P-gp function.

## INTRODUCTION

P-glycoprotein (P-gp) is a product encoded by the *mdr*1 gene which confers the multidrug resistance (MDR) phenotype to tumor cells. The P-gp in multidrug-resistant cells actively transports antitumor agents such as vincristine (VCR), doxorubicin (Dox), *etc*, outside the cells, leading to a decrease in the intracellular accumulation of antitumor agents. Furthermore, the P-gp is expressed in various normal tissues such as adrenal, kidney, liver, and the luminal side of the capillary endothelial cells that comprise the blood-brain barrier (BBB). P-gp expresses in the BBB functions actively as an efflux pump and blocks the accumulation of many therapeutic drugs in brain tissues in the physiological state, resulting in decreased permeability into the brain and the failure of therapy to the brain disease. The development of compounds specifically inhibiting P-gp functional activity in BBB might contribute to therapeutic progress[1].

A variety of inhibitors of P-gp transport function have been identified, and some compounds currently in clinical use are being tested for modulation of MDR [eg, cyclosporin A (CsA), verapamil (Ver), and vincristine (VCR)]. All of these drugs have dose-limiting side effects due to their intrinsic stereospecific pharmacological activities. Other compounds are being specifically developed for clinical use as P-gp inhibitors for MDR reversal (eg, PSC-833, a non-immunosuppressive analog of cyclosporin)[2]. Some principles extracted from Chinese herbal medicine have also been reported to be capable of reversing MDR in tumor cells[3]. In order to increase the delivery of therapeutically desirable P-gp substrates to the brain and improve the therapeutics of

[1] Project supported by the National Natural Science Foundation of China, No 39870885 and by the National 863 Program Foundation of China, No 2001AA234011.
[2] Correspondence to Dr HE Ling.
Phn 86-25-327-1322. E-mail hexyz@263.net
Received 2001-09-24 Accepted 2002-04-05

ISSN 1671-4083 Acta Pharmacol Sin 中国药理学报 2002 Jul; 23 (7)
E-mail aps@mail.shcnc.ac.cn Phn/Fax 86-21-6474-2629

various central nervous system diseases, such as brain tumors and schizophrenia, *etc*, it is particularly necessary to study the effects of these inhibitors on drug distribution at the BBB and develop novel effective P-gp reversal agents with low toxicity in the BBB[4].

The ability to quantitatively assess the functional activity of P-gp in brain capillary endothelial cells (BCEC) will be important for determining the interactions of various compounds with P-gp and predicting the impact of these interactions on BBB permeability. The fluorescent dye, rhodamine123 (Rh123), a P-gp substrate can be used to assess the functional activity of P-gp in the BBB and to predict the effecus that inhibition of P-gp on BBB function[5]. In order to search for novel effective P-gp reversal agents in the BBB, this study examined the effects of some known MDR-reversing agents in tumor cells and 8 principles from Chinese herbal medicine on the accumulation of Rh123 in primary cultured bovine BCEC monolayers as an *in vitro* BBB system.

## MATERIALS AND METHODS

**Materials** Anti-P-gp monoclonal antibody C219 was donated by Dr WANG Jian-Xin (Cheron Co, USA). CsA, VCR, flunarizine (Flu), azithromycin (Azi) were gifts from Dr LIU Xiao-Dong (China Pharmaceutical University). Dox was a gift from Prof GUO Qing-Long (China Pharmaceutical University). Eight principles: tetrandrine (Tet), *dl*-tetrahydropalmatine (*dl*-THP), dauricine (DRC), berbamine (BBM), daurisoline (DRS), berberine (BBR), *l*-tetrahydropalmatine (*l*-THP), and tetramethylpyrazine (TMP) were kindly donated by Prof HUA Wei-Yi (China Pharmaceutical University), purity >98 %. Ver, F-12 nutrient mixture (Ham), Dulbecco's modified Eagle's medium (DMEM), rhodamine123, and collagenase Ⅱ were purchased from Sigma Co. All other chemicals were of analytic grade and commercially available.

**Isolation of bovine brain capillaries and culture of BCEC** Bovine brain capillaries were isolated from cerebral gray matter of bovine brain by a method described previously[6]. Examination of the purity of the capillary preparation by microscopy and assaying the relative specific activity of the marker enzyme γ-glutamyltransferase (γ-GTase) revealed that the preparation was composed of capillary segments with less than 2 % of contamination cells and enriched 14.7-fold in γ-GTase specific activity over the brain homogenate. The capillary preparation was resuspended in 10 volumes of 0.1 % (w/v) collagenase Ⅱ in phosphate buffered saline solution (PBS) and incubated at 37 ℃ for 30 min. The suspension was centrifuged at 1000 × *g* for 10 min at 4 ℃, and the pellet was washed twice with PBS. The pellet of BCEC was resuspended in culture medium with the following composition (v/v): 45 % DMEM, 45 % F-12 nutrient mixture (Ham), 10 % horse serum, heparin (100 mg/L), streptomycin (100 mg/L), penicillin (100 mg/L), gentamycin (50 mg/L), and amphotericin B (2.5 mg/L), seeded at cell density of 50 000/cm$^2$ on collagen-coated 24-well tissue culture plates, and cultured at 37 ℃ with 95 % air and 5 % $CO_2$. Media was replaced every 2 – 3 d. The BCEC monolayers were used in the cellular accumulation studies after reaching confluence (10 – 12 d) as determined by visual inspection of the monolayers under an inverted light microscope.

**Rhodamine123 cellular accumulation** Cellular accumulation experiments were performed in assay buffer (pH 7.4) of the following composition (mmol/L): NaCl 122, $NaHCO_3$ 25, KCl 3, $MgSO_4$ 1.2, $K_2HPO_4$ 0.4, $CaCl_2$ 1.4, HEPES 10, and glucose 10. The culture media was removed and the BCEC monolayers were pre-incubated in assay buffer (37 ℃) for 30 min. After pre-incubation, the assay buffer was removed and replaced with 0.5 mL of assay buffer containing Rh123 (1 – 20 μmol/L). The cellular accumulation of Rh123 was examined at 37 ℃ over various periods (10 – 120 min) in the presence or absence of the test agents. The Rh123 cellular accumulation studies were terminated by removing the assay buffer solution and washing the BCEC monolayers three times with 1.0 mL of ice-cold PBS. The BCEC were solubilized in NaOH (0.2 mol/L) and aliquots of the cell solution were removed for analysis of Rh123 and protein content. The cellular accumulation of Rh123 was determined quantitatively by fluorescence spectrophotometry. Samples (250 μL) of the solubilized cell solutions were diluted to 1 mL with PBS. Sample fluorescence was measured using a HITACHI MPF-4 Fluorescence Spectrophotometer (excitation wavelengh 492 nm; emission wavelengh 525 nm). The concentration of Rh123 in each sample was determined from the fluorescence measurements by the construction of a Rh123 standard curve[5]. The amount of Rh123 in the cell samples were standardized with the amount of protein in each sample as determined by Coomassie brilliant blue

G-250 dye binding method and expressed as $\mu mol \cdot g^{-1}$ protein[7].

**Reversibility of BCEC permeability** The effects of 6 P-gp reversal agents in different structure, which inhibited the functional activity of P-gp and increased the cellular accumulation of Rh123 in BCEC with marked effectiveness, on Rh123 uptake at various intervals after first treatment were examined to determine whether the response of BCEC to these agents were reversible. In these studies, BCEC were pretreated with CsA, Tet, Ver ,Flu, Azi, or *dl*-THP (10 μmol/L) for 2 h, respectively, and then these agents were removed and replaced with culture media for 12, 24, 36, or 48 h, respectively, before performing the Rh123 accumulation study[8].

**Data analysis** All the results were represented as $\bar{x} \pm s$. Student's *t*-test was used for statistical analysis and statistical significance was defined as $P < 0.05$ or $P < 0.01$.

## RESULTS

**Time course of Rh123 accumulation** The time course of Rh123 uptake by BCEC at 37 ℃ and pH 7.4. The accumulation of Rh123 was time-dependent and the steady-state was attained by 90 min, the steady-state uptake amount of Rh123 was $(3.1 \pm 0.4)$ $\mu mol \cdot g^{-1}$ protein. Accordingly, the uptake at 90 min was selected to evaluate the transport characteristics of Rh123 in the following experiments (Fig 1).

**Concentration-dependent accumulation of Rh123** The cellular accumulation of various concentrations of Rh123 (1 – 20 μmol/L) was examined in BCEC either alone or in the presence of the well-known P-gp modifying agent, CsA. The amount of cellular Rh123 was increased in a concentration-dependent manner in both the control and CsA (5 μmol/L)-treated BCEC. The effect of CsA on Rh123 accumulation in BCEC was dependent on the concentration of Rh123 present in the assay buffer, at concentration below Rh123 3 μmol/L almost no effect could be seen, while at higher concentrations (10 μmol/L) as much as 3.7 fold increases in accumulation in CsA-treated group was shown (Fig 2). Accordingly, the concentration of Rh123 was fixed at 10 μmol/L in the following experiments.

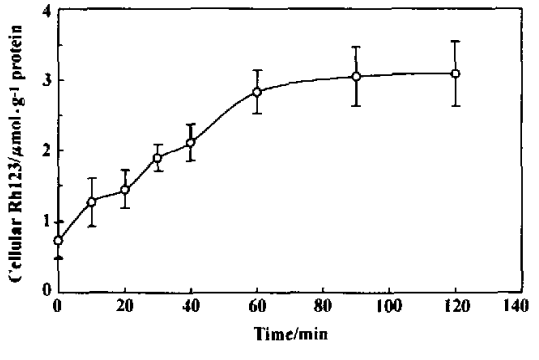


**Fig 1. Time-dependent accumulation of Rh123 in BCEC. Cells were incubated with assay buffer containing Rh123 (10 μmol/L) at 37 ℃. $n = 3$ experiments (each 5 wells). $\bar{x} \pm s$.**

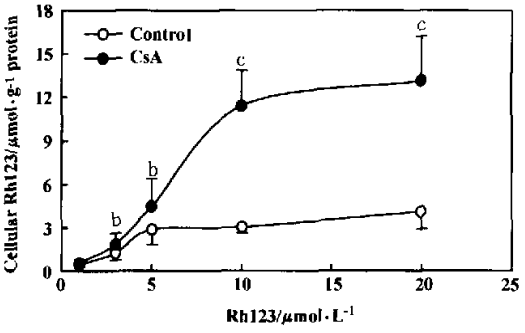


**Fig 2. Concentration-dependent accumulation of Rh123 in BCEC. The amount of Rh123 was determined following a 90 min incubation period in the absence or presence of CsA (5 μmol/L). $n = 3$ experiments (each 5 wells). $\bar{x} \pm s$. $^bP < 0.05$, $^cP < 0.01$ *vs* control (no CsA).**

**Effects of MDR-reversing agents and 8 principles on cellular accumulation of Rh123 in BCEC** The results showed that the anti-P-gp monoclonal antibody C219 100 μg/L increased cellular accumualtion of Rh123 by 287 %, and all of test compounds increased the cellular accumulation of Rh123 in a concentration-dependent manner. The rank order of these agents in increasing Rh123 accumulation in BCEC was CsA > Tet > VCR ≈ Flu > *dl*-THP > DRC > Azi > Ver ≈ BBM > DRS > BBR ≈ Dox > *l*-THP > TMP (Tab 1). Unlike the BCEC, there was no remarkable increase in Rh123 accumultion by these agents at concentration of 10 μmol/L in human umbilical vein endothelial cells (HUVEC) that do not express P-gp (data not shown).

ISSN 1671-4083 Acta Pharmacol Sin 中国药理学报 2002 Jul; 23 (7)
E-mail aps@mail.shcnc.ac.cn Phn/Fax 86-21-6474-2629

**Reversibility of BCEC permeability induced by P-gp reversal agents** The effects of CsA, Tet, Ver, Flu, Azi, or *dl*-THP on Rh123 uptake at various intervals after first treatment were examined to determine whether the response of BCEC to these agents were reversible. The increase in BCEC permeability induced by all of 6 P-gp reversal agents was reversible. When CsA, Tet, Ver, Flu, Azi, or *dl*-THP-pretreated BCEC were examined at 48, 36, 24, 36, 36, or 12 h, respectively, after removing the agent, the amount of cellular Rh123 accumulation in BCEC returned to control levels ( no drug treatment). Finally, exposing the BCEC to a second treatment of these agents resulted in marked increase in Rh123 accumulation again (Fig 3).

## DISCUSSION

P-gp, which functions as an ATP-dependent pump that transports drugs out of MDR tumor cells, also exists in BCEC. It localizes in the luminal membrane of BCEC and transports Rh123 (a P-gp substrate) out of cells. As observed in MDR tumor cells, the transport of Rh123 mediated by P-gp is inhibited by various MDR-reversing agents[2,5,9,10].

In this study, the accumulation of Rh123 in BCEC was used to quantitatively examine P-gp functional activity in the BBB to screen novel effective P-gp reversal agents[11]. Tab 1 showed the effects of various agents, which reversed drug resistance *in vitro* and specifically bound to P-gp of MDR tumor cells, as well as 8 principles extracted from Chinese herbal medicine on the steady-state uptake of Rh123 by BCEC. There were some reports about the modulation of MDR by these principles recently[3,12-14]. We found that all of test MDR-reversing agents and 8 principles from Chinese herbal medicine could increase the cellular Rh123 in BCEC in concentration-dependent manner with different effectiveness. Especially, Tet, *dl*-THP, and DRC, 3 isoquinoline alkaloids isolated from herbs, showed greater effectiveness in inhibition of P-gp functional activity than Ver, the well-known standard MDR-reversing agent. Tet was the most potent P-gp inhibitor among the 3 principles and even more effective than VCR. The results supplied some clues and evidence for development of novel effective P-gp reversal agents in BBB, and indicated that some principles with low toxicity extracted

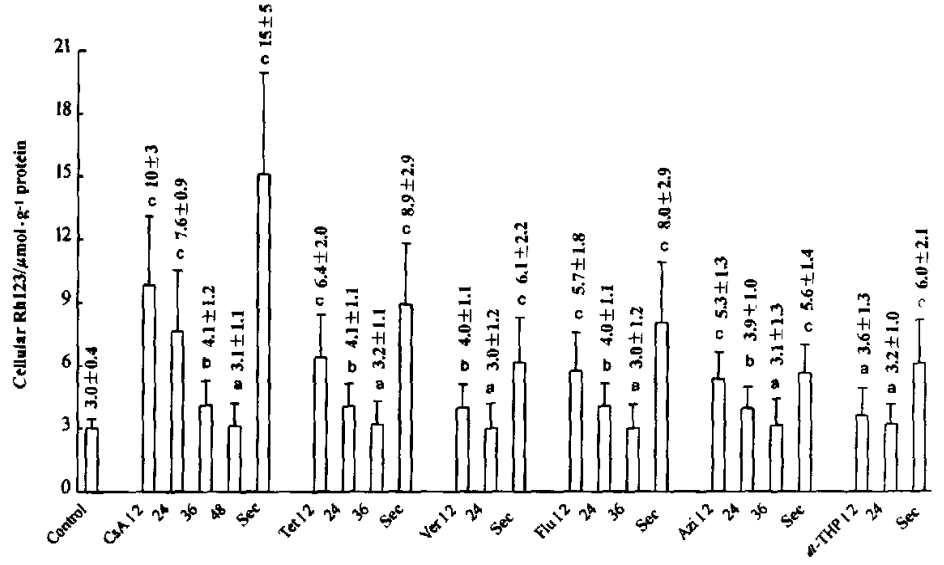


**Fig 3. Reversibility of P-gp reversal agents induced effects on BCEC permeability. BCEC were treated with P-gp reversal agent (10 μmol/L) for 2 h, and then, the agent was removed. The cellular Rh123 accumulation were examined at various period (12, 24, 36, or 48 h) after removing the agent. Finally, the BCEC were exposed to a second treatment (sec) of the agent and the cellular Rh123 were measured. $n = 3$ experiments (each 4 wells). $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* control (no drug treatment).**

**Tab 1. Effects of some MDR reversal agents and 8 principles on intracellular Rh123 accumulation in BCEC. Cells were preincubated with each compound at 37 ℃ for 30 min and then the accumulation of Rh123 (10 μmol/L) was measured for 90 min. $n = 3$ experiments (each 5 wells). $\bar{x} \pm s$. $^bP < 0.05$, $^cP < 0.01$ *vs* control.**

| Compounds/μmol·L$^{-1}$ | | Cellular Rh123 /μmol·g$^{-1}$ protein | Increase of cellular Rh123/% |
|---|---|---|---|
| Control | | 3.1±0.4 | |
| C219 | 100 μg·L$^{-1}$ | 12±4$^c$ | 287 |
| Cyclosporine A | 0.5 | 4.1±1.2$^c$ | 34 |
| | 1.0 | 4.6±1.8$^c$ | 51 |
| | 2.5 | 7±3$^c$ | 140 |
| | 5.0 | 11±2$^c$ | 270 |
| | 10 | 14±4$^c$ | 346 |
| Verapamil | 1.0 | 3.7±1.0 | 21 |
| | 2.5 | 4.0±1.0$^c$ | 30 |
| | 5.0 | 4.4±2.0$^c$ | 43 |
| | 10 | 5.7±1.9$^c$ | 87 |
| Vicristine | 1.0 | 3.9±1.0$^c$ | 29 |
| | 2.5 | 4.5±1.1$^c$ | 47 |
| | 5.0 | 5.5±1.3$^c$ | 79 |
| | 10 | 7.2±1.5$^c$ | 136 |
| Doxorubicin | 2.5 | 4.0±1.2$^c$ | 30 |
| | 5.0 | 4.3±1.8$^c$ | 42 |
| | 10 | 5.1±1.2$^c$ | 67 |
| | 20 | 5.9±1.6$^c$ | 93 |
| Flunarizine | 1.0 | 4.0±1.1$^c$ | 31 |
| | 2.5 | 4.4±1.4$^c$ | 43 |
| | 5.0 | 5.4±1.5$^c$ | 76 |
| | 10 | 7.0±2.2$^c$ | 129 |
| Azithromycin | 1.0 | 3.7±1.1 | 21 |
| | 2.5 | 4.2±1.3$^c$ | 38 |
| | 5.0 | 4.9±1.3$^c$ | 59 |
| | 10 | 5.9±1.9$^c$ | 92 |
| Tetrandrine | 1.0 | 4.2±1.1$^c$ | 37 |
| | 2.5 | 4.9±1.5$^c$ | 61 |
| | 5.0 | 6.9±2.3$^c$ | 125 |
| | 10 | 9±3$^c$ | 203 |
| Daurisoline | 1.0 | 3.6±1.2 | 19 |
| | 2.5 | 4.0±1.5$^c$ | 32 |
| | 5.0 | 4.3±1.2$^c$ | 41 |
| | 10 | 5.3±2.1$^c$ | 75 |
| Dauricine | 1.0 | 3.9±1.1 | 29 |
| | 2.5 | 4.3±1.5$^c$ | 41 |
| | 5.0 | 4.9±1.7$^c$ | 62 |
| | 10 | 6.2±2.0$^c$ | 103 |
| *dl*-THP | 1.0 | 4.0±1.6$^c$ | 32 |
| | 2.5 | 4.3±1.2$^c$ | 41 |
| | 5.0 | 5.0±1.6$^c$ | 64 |
| | 10 | 6.6±2.1$^c$ | 115 |
| *l*-THP | 2.5 | 3.8±1.4 | 23 |
| | 5.0 | 4.1±1.4$^c$ | 35 |
| | 10 | 5.0±1.1$^c$ | 63 |
| | 20 | 5.4±1.8$^c$ | 77 |
| Berbamine | 1.0 | 3.6±1.4 | 19 |
| | 2.5 | 3.9±1.4 | 27 |
| | 5.0 | 4.3±1.3$^c$ | 41 |
| | 10 | 5.5±1.9$^c$ | 81 |
| Berberine | 1.0 | 3.6±1.0 | 19 |
| | 2.5 | 3.9±1.5 | 29 |
| | 5.0 | 4.2±1.4$^c$ | 38 |
| | 10 | 5.1±2.0$^c$ | 67 |
| TMP | 2.5 | 3.7±0.9 | 20 |
| | 5.0 | 4.0±1.3$^c$ | 31 |
| | 10 | 4.7±1.6$^c$ | 54 |
| | 20 | 5.2±1.6$^c$ | 69 |

from medicinal herbs, such as some isoquinoline alkaloids could be explored for clinical use as P-gp reversal agents in BBB.

Furthermore, we have shown that the effects of these P-gp reversal agents on BCEC permeability were reversible. In other words, the P-gp functional activity in BCEC which were pretreated with various modulators could return to control level at various periods after removing these agents. As the results suggested that, at the proper dosage, administration of P-gp reversal agent to patients could help enhancing the response of brain diseases to therapeutic drugs without permanent modifying the intrinsic level of P-gp function in BBB. When the reversal agent was withdrawn, the physiological function of P-gp returned to normal level. The reversibility of P-gp reversal agent-induced effects on BBB permeability might prove to be of clinical interest.

## REFERENCES

1 Tsuji A, Terasaki T, Takabatake Y, Tenda Y, Tamai I, Yamashima T. P-glycoprotein as the drug efflux pump in primary cultured bovine brain capillary endothelial cells. Life Sci 1992; 51: 1427-37.

2 Robert J. Multidrug resistance reversal agents. Drugs Future 1997; 22: 149-58.

3 Tian H, Pan QC. Modulation of multidrug resistance by three bisbenzyl-isoquinolines in comparison with verapamil. Acta Pharmacol Sin 1997; 18: 455-8.

4 Cordon-Cardo C, O'Brien JP, Casals D, Biedler JL, Melamed MR. Multidrug-resistance gene (P-glycoprotein) is expressed by endothelial cells at blood-brain barrier sites. Proc Natl Acad Sci USA 1989; 86: 695-8.

5 Fontaine M, Elmquist WF, Miller DW. Use of rhodamine 123 to examine the functional activity of P-glycoprotein in primary cultured brain microvessel endothelial cell monolayers.

ISSN 1671-4083 Acta Pharmacol Sin 中国药理学报 2002 Jul; 23 (7)
E-mail aps@mail.shcnc.ac.cn Phn/Fax 86-21-6474-2629

Life Sci 1996; 59: 1521 – 31.
6 Zhang Y, Liu GQ. Sodium and chloride-dependent high and low-affinity uptakes of GABA by brain capillary endothelial cells. Brain Res 1998; 808: 1 – 7.
7 Bradford MM. A rapid sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem 1976; 72: 248 – 54.
8 Mark KS, Miller DW. Increased permability of primary cultured brain microvessel endothelial cell monolayers following TNF-α exposure. Life Sci 1999; 64: 1941 – 53.
9 Twentyman PR, Rhodes T, Rayner S. A comparison of rhodamine 123 accumulation and efflux in cells with P-glycoprotein-mediated and MRP-associated multidrug resistance phenotypes. Eur J Cancer 1994; 30A: 1360 – 9.
10 Hegmann EJ, Bauer HC, Kerbel RS. Expression and functional activity of P-glycoprotein in cultured cerebral capillary endothelial cells. Cancer Res 1992; 52: 6969 – 75.
11 Audus KL, Borchardt RT. Characterization of an *in vitro* blood-brain barrier model system for studying drug transport and metabolism. Pharm Res 1986; 3: 81 – 7.
12 Shiraishi N, Akiyama S, Nakagawa M, Kobayashi M, Kuwano M. Effects of bisbenzylisoquinoline alkaloids on multidrug resistance in KB human cancer cells. Cancer Res 1987; 47: 2413 – 6.
13 Pan QC, Tian H. Reversal of multidrug resistence by various principles from Chinese herbal medicine. Chin Sci Bull 1995; 40: 1901 – 5.
14 Jette L, Murphy GF, Leclerc JM. Interaction of drugs with P-glycoprotein in brain capillaries. Biochem Pharmacol 1995; 50: 1701 – 9.

## 多种中草药单体对脑微血管内皮细胞内罗丹明 123 积累的影响

何 玲[2], 刘国卿 RZ A
(中国药科大学药理教研室, 南京 210009, 中国)

**关键词** P-糖蛋白; 血脑屏障; 多种抗药性; 氧杂蒽类; 异喹啉类

**目的**: 寻找新型有效的血脑屏障 P-糖蛋白逆转剂. **方法**: 通过测定各化合物对牛脑微血管内皮细胞内罗丹明 123 积累的影响来考查它们对 P-糖蛋白的功能性作用, 以此筛选血脑屏障上的 P-糖蛋白逆转剂. **结果**: 各化合物浓度依赖性地增加胞内 Rh123 的累积浓度, 作用强弱顺序为: 环孢素 A (CsA) > 粉防己碱(Tet) > 长春新碱(VCR) ≈ 氟桂利嗪(Flu) > 延胡索乙素(*dl*-THP) > 蝙蝠葛碱(DRC) > 阿齐霉素(Azi) > 维拉帕米(Ver) ≈ 小檗胺(BBM) > 蝙蝠葛苏林碱(DRS) > 小檗碱(BBR) > 阿霉素(Dox) > 左旋四氢巴马汀(*l*-THP) > 川芎嗪(TMP). 其中 CsA、Tet、Ver、Flu、Azi 和 *dl*-THP 对胞内罗丹明 123 的累积的影响是可逆的. **结论**: 多种中药单体, 如某些异喹啉类生物碱能逆转血脑屏障上 P-糖蛋白的功能, 而不使血脑屏障上 P-糖蛋白的固有水平发生永久性改变.

(责任编辑 朱倩荟)