Effect of resveratrol on baroreceptor activity of carotid sinus in anesthetized male rats

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Abstract: This study is to evaluate the effect of resveratrol on carotid baroreceptor activity (CBA). The functional curve of carotid baroreceptor (FCCB) was constructed and the functional parameters of carotid baroreceptor were measured by recording sinus nerve afferent discharge in anesthetized male rats with perfused isolated carotid sinus. Resveratrol (30, 60 and 120 μmol·L^{-1}) inhibited CBA, which shifted FCCB to the right and downward. There was a marked decrease in peak slope (PS) and peak integral value (PIV) of carotid sinus nerve charge in a concentration-dependent manner. Pretreatment with N^{ω}-nitro-*L*-arginine methyl ester (*L*-NAME, 100 μmol·L^{-1}), an inhibitor of nitric oxide synthase (NOS), eliminated the inhibitory effect of resveratrol. Pretreatment with Bay K8644 (an agonist of L-type calcium channel, 500 nmol·L^{-1}) abolished the effect of resveratrol on CBA. A potent inhibitor of tyrosine phosphatase (sodium orthovanadate, 1 mmol·L^{-1}) did not influence the effect of resveratrol on CBA. Resveratrol inhibits carotid baroreceptor activity, which may be mediated by the locally released NO and decreased calcium influx. Several studies have showed a cardioprotective effect of resveratrol, with the penetrating study of resveratrol, it may show a potential value in the clinical treatment of cardiovascular disease as an alternative medicine.

Key words: resveratrol; baroreceptor; *L*-NAME; Bay K8644; protein tyrosine kinase

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白藜芦醇对麻醉大鼠颈动脉窦压力感受器的作用

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摘要: 在隔离灌流左侧颈动脉窦区的麻醉大鼠上观察了白藜芦醇对颈动脉窦压力感受器活动的影响。隔离灌流麻醉大鼠的颈动脉窦区,同时记录窦神经放电,并绘制压力感受器活动的机能曲线。白藜芦醇(30, 60及120 μmol·L^{-1})隔离灌流颈动脉窦区时,压力感受器活动的机能曲线向右下方移位,曲线的斜率以及窦神经放电的最大积分值显著下降,且其变化呈一定的剂量依赖性。预先应用NO合酶抑制剂(*L*-NAME, 100 μmol·L^{-1})可完全消除白藜芦醇对压力感受器活动的抑制作用;预先应用钙通道的开放剂(Bay K8644, 500 nmol·L^{-1})可以取消白藜芦醇的抑制作用;预先应用正矾酸钠(sodium orthovanadate, 1 mmol·L^{-1})后,对白藜芦醇抑制压力感受器活动的作用无影响。白藜芦醇对大鼠颈动脉窦压力感受器活动有抑制作用,此作用可能与局部NO的释放及减弱牵张敏感性通道介导的钙离子内流有关。

关键词: 白藜芦醇; 压力感受器; *L*-NAME; Bay K8644; 蛋白酪氨酸激酶

Resveratrol (3, 4′, 5-trihydroxystilbene) is a naturally occurring phenolic substance present in a variety of plants such as *Polygonum cuspidatum* ("Kojokon" in Japanese) roots and grapes[1-3]. Resveratrol exhibits a wide range of biological effects, including cancer chemoprevention, antioxidative,

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antiplatelet, antifungal, anti-inflammatory, phytoestrogenic and cardioprotective activities[2-5]. Since resveratrol is found in high concentration in some red wine[6], interest in this compound has expanded. Numerous epidemiologic studies have showed an inverse correlation between red wine consumption and incidence of cardiovascular disease[1].

Several recent studies determined the cardioprotective activities of resveratrol[7]. Both in acute and in chronic experiment, resveratrol protects the cardiovascular system against ischemic-reperfusion injury, promotes vasorelaxation, maintains the intact endothelium, exhibits antiatherosclerotic properties and inhibits the low-density lipoprotein oxidation, suppresses the platelet aggregation and exhibits estrogen like action[8]. Zhang et al[9] showed that resveratrol inhibited $I_{Ca\text{-}L}$ in rat ventricular myocytes mainly by inhibiting the activation of L-type calcium channels and slowing down the recovery of calcium channels from inactivation. Additionally, resveratrol can induce vasorelaxations which may relate to inhibition of Ca^{2+} influx and Ca^{2+} release from intracellular stores, and the relaxing response of resveratrol is endothelium-dependent in part[10]. Thus resveratrol may show a potential clinical value in the treatment of cardiovascular disease as an alternative medicine.

It is well known that baroreflex is the major way of blood pressure modulation. Whether resveratrol affects the carotid baroreceptor activity (CBA) remains to be clarified. The aim of our study is to observe the action of resveratrol on CBA in anesthetized male rats with perfused isolated carotid sinus through direct recording of carotid sinus nerve activity (CSNA), and to elucidate the mechanism involved.

Materials and methods

Drugs Resveratrol, *L*-NAME, Bay K8644 and sodium orthovanadate were purchased from Sigma. Resveratrol was dissolved with dimethyl sulphoxide. The final concentration of dimethyl sulphoxide in the perfusing solution was lower than 0.02% (*v*/*v*). No change was observed in the CBA during perfusion with the final concentration of dimethyl sulphoxide. *L*-NAME and sodium orthovanadate were dissolved in saline. Bay K8644 was dissolved in 99% ethyl alcohol. No change of CBA was observed during perfusion with ethyl alcohol (1∶2 000).

General surgical procedure Sprague-Dawley rats (♂, 300 - 340 g, n = 36, Grade II, Certificate No. 609086), obtained from the Experimental Animal Center of Hebei Province, were anesthetized with 25% urethane (1.0 g·kg^{-1}, ip). In each rat, the trachea was cannulated for ventilation. Body temperature was maintained at 37 - 38 ℃ throughout the experiment.

Perfusion of left isolated carotid sinus The perfusion of isolated carotid sinus area was carried out by using a method modified by our laboratory[11]. The intrasinus pressure (ISP) was monitored by using a pressure transducer (MPU-0.5 A; Nihon Kohden) connected to the inlet tube. Then ISP was controlled by using a peristaltic pump and was altered in a stepwise manner.

After perfusion of the left carotid sinus, the ISP was kept at 100 mmHg for 20 min and was then lowered to 0 mmHg rapidly. From this point, the ISP was elevated to 250 mmHg via a pulsatile ramp by regulating the speed of the peristaltic pump and each step of the staircase changed the ISP by 30 mmHg and lasted for 15 s, which was automatically controlled by a program designed by our laboratory[12].

Recording of sinus nerve afferent discharge The left carotid sinus nerve was cut near the glossopharyngeal nerve and desheathed carefully. The isolated sinus nerve and surrounding structures were immersed in warm (37 ℃) liquid paraffin to avoid drying of the tissues. The sinus nerve was placed on a bipolar platinum electrode and the bioelectrical signal was recorded on a polygraph (RM-6240; Chengdu Instrument Factory), with an integral time of 5 s. ISP and discharge of sinus nerve were recorded synchronously and at the end of the experiment, the integral of sinus nerve activity (ISNA) was obtained and measured.

Experimental protocols By perfusing the left carotid sinus with K-H solution and elevating the ISP, a functional curve for the ISP-ISNA relationship was constructed, and the functional parameters of carotid baroreceptor such as threshold pressure (TP), saturation pressure (SP), peak slope (PS), peak integral value (PIV) and operating range (OR) were determined. TP was the ISP at which ISNA began to increase by 15% in response to the increase of the ISP. SP was the ISP at which ISNA just showed no further increase with an increase in the ISP. OR was calculated as SP minus TP. Before administration of the drugs, the K-H solution was used as a control. Four experimental treatments were used. (1) To test the effect of resveratrol on CBA (n = 18), the ISP was

fixed at 100 mmHg for 20 min with K-H solution as a control. The functional curve of carotid baroreceptor (FCCB) was drawn. Then K-H solution containing resveratrol (30, 60 and 120 μmol• L^{-1}) was used to perfuse the isolated carotid sinus for 50 min, then the parameters were measured again. Finally, the carotid sinus was perfused with K-H solution to wash out resveratrol. (2) To test the effect of *L*-NAME (100 μmol• L^{-1}) on the actions of resveratrol (n = 6), FCCB was drawn and parameters were examined following the application of resveratrol before and after pretreatment with *L*-NAME for 20 min. (3) To test the effect of Bay K8644 (500 nmol• L^{-1}) on the actions of resveratrol (n = 6), relating parameters were examined following the application of resveratrol before and after pretreatment with Bay K8644 for 20 min. (4) To test the effect of sodium orthovanadate (1 mmol• L^{-1}) on the CBA (n = 6), relating parameters were examined following the application of resveratrol before and after pretreatment with sodium orthovanadate for 20 min.

Statistics All data are expressed as $\bar{x} \pm s$. The differences between groups of means were assessed by one-way ANOVA and further analyzed using the Student-Newman-Kuels test. $P < 0.05$ was considered statistically significant.

Results

1 Effect of resveratrol on carotid baroreceptor activity

Perfusing the left carotid sinus with K-H solution and elevating the ISP from 0 to 250 mmHg in a stepwise manner, ISNA was increased. Resveratrol induced obvious changes in FCCB, which appeared approximately 20 min after perfusing the isolated carotid sinus with K-H solution containing resveratrol, and disappeared 30 - 60 min after washout. There was no difference in CBA parameters among controls. Compared with the control group, resveratrol decreased PIV and PS in a concentration-dependent manner, and increased TP and SP, shifting FCCB downward and to the right (Table 1, Figure 1). The functional curve was fitted using Origin 6.0 procedures. The effects described indicate that resveratrol exerts an inhibitory effect on ISNA (Figure 2).

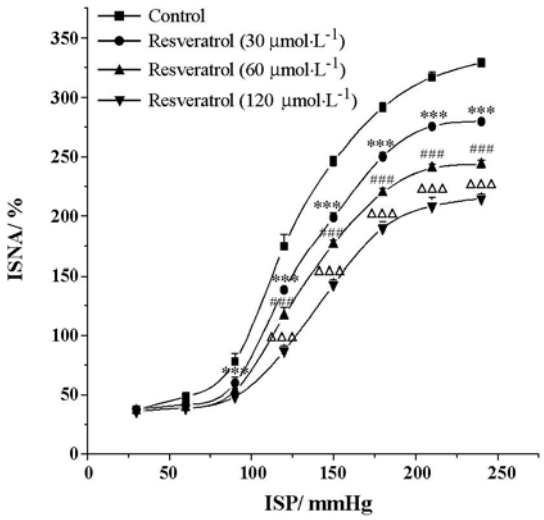

Figure 1 Changes in functional curves of carotid baroreceptor during intrasinus perfusion with different doses of resveratrol in rats. n = 18, $\bar{x} \pm s$. $^{***}P < 0.001$ *vs* control; $^{\#\#\#}P < 0.001$ *vs* resveratrol (30 μmol• L^{-1}); $^{\triangle\triangle\triangle}P < 0.001$ *vs* resveratrol (60 μmol• L^{-1}). ISP: Intrasinus pressure; ISNA: Integral of sinus nerve activity

2 Effects of *L*-NAME, Bay K8644 and sodium orthovanadate on resveratrol responses

L-NAME (100 μmol• L^{-1}) did not affect FCCB ($P > 0.05$), but it abolished the actions of resveratrol (60 μmol• L^{-1}) on FCCB. Bay K8644 (500 nmol• L^{-1}) did not affect FCCB ($P > 0.05$), but it completely blocked the actions of resveratrol (60 μmol•

Table 1 Effect of resveratrol on the functional parameters of carotid baroreceptor in the rats

Group	Dose/μmol• L^{-1}	TP/mmHg	SP/mmHg	OR/mmHg	PS	PIV/%
Control		45.1 ±2.0	157.5 ±1.9	113.3 ±1.5	3.00 ±0.06	329.0 ±3.9
Resveratrol	30	50.4 ±1.1**	165.0 ±1.4***	114.8 ±1.5	2.58 ±0.11***	279.7 ±1.6***
	60	58.1 ±4.6$^{\#\#\#}$	171.5 ±2.1$^{\#\#\#}$	115.3 ±1.2	2.37 ±0.09$^{\#\#\#}$	243.5 ±3.7$^{\#\#\#}$
	120	68.1 ±3.7$^{\triangle\triangle\triangle}$	184.5 ±1.1$^{\triangle\triangle\triangle}$	17.0 ±4.4	2.05 ±0.07$^{\triangle\triangle\triangle}$	214.7 ±3.5$^{\triangle\triangle\triangle}$

K-H solution was used as control, intrasinus pressure of isolated carotid sinus was fixed at 100 mmHg for 20 min as the control, measured the functional parameters of baroreceptor, then K-H solution containing resveratrol was used to perfuse the carotid sinus for 50 min, the parameters were measured. n = 6, $\bar{x} \pm s$. $^{**}P < 0.01$, $^{***}P < 0.001$ *vs* control; $^{\#\#\#}P < 0.001$ *vs* resveratrol (30 μmol• L^{-1}); $^{\triangle\triangle\triangle}P < 0.001$ *vs* resveratrol (60 μmol• L^{-1}). TP: Threshold pressure; SP: Saturation pressure; OR: Operating range; PS: Peak slope; PIV: Peak integral value

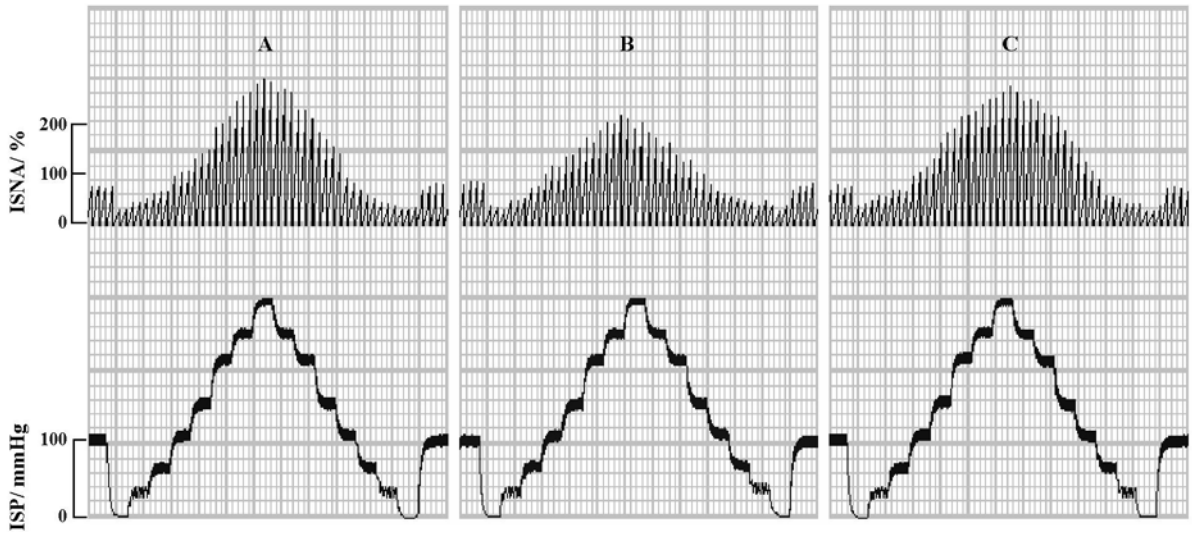

Figure 2　Original recording showing the responses of ISNA to intrasinus perfusion with resveratrol (60 μmol· L^{-1}). A: Control; B: Resveratrol (60 μmol· L^{-1}); C: Washout

Table 2　Effects of *L*-NAME (100 μmol· L^{-1}), Bay K8644 (500 nmol· L^{-1}) and sodium orthovanadate (Na_3VO_4, 1 mmol· L^{-1}) on the response of carotid baroreceptor induced by perfusing carotid sinus with resveratrol (60 μmol· L^{-1}) in the rats

Group	TP/mmHg	SP/mmHg	OR/mmHg	PS	PIV/%
Control	45.3 ±2.1	156.0 ±2.1	111.5 ±1.8	3.02 ±0.05	327.8 ±2.9
Resveratrol	57.6 ±1.4***	171.7 ±1.9***	114.5 ±1.1**	2.37 ±0.02***	244.2 ±2.8***
L-NAME	45.0 ±1.8$^{+###}$	156.3 ±2.4$^{+###}$	112.0 ±1.7$^{+##}$	3.03 ±0.08$^{+###}$	329.2 ±6.9$^{+###}$
L-NAME + resveratrol	45.8 ±1.6$^{###}$	157.0 ±1.4$^{###}$	112.0 ±1.3$^{##}$	2.95 ±0.05$^{###}$	330.8 ±3.5$^{###}$
Control	45.1 ±1.4	156.2 ±1.5	111.8 ±1.9	3.01 ±0.03	329.0 ±2.4
Resveratrol	57.6 ±1.0**	171.8 ±1.2***	114.7 ±1.4**	2.37 ±0.04***	240.8 ±3.6***
Bay K8644	45.0 ±1.2$^{+###}$	155.7 ±1.6$^{+###}$	111.5 ±0.7$^{+##}$	2.96 ±0.06$^{+###}$	333.2 ±5.8$^{+###}$
Bay K8644 + resveratrol	45.5 ±1.1$^{###}$	156.3 ±1.0$^{###}$	111.7 ±2.0$^{##}$	2.96 ±0.05$^{###}$	329.7 ±4.7$^{###}$
Control	45.0 ±1.9	155.7 ±1.8	111.5 ±2.1	2.96 ±0.10	328.5 ±4.9
Resveratrol	57.8 ±1.4***	172.0 ±1.4***	114.7 ±1.0**	2.38 ±0.07***	240.0 ±4.2***
Na_3VO_4	46.2 ±2.1$^{+###}$	156.8 ±1.2$^{+###}$	111.5 ±2.1$^{+##}$	2.98 ±0.07$^{+###}$	331.8 ±2.1$^{+###}$
Na_3VO_4 + resveratrol	57.3 ±1.2$^{***\triangle\triangle\triangle}$	172.2 ±1.5$^{***\triangle\triangle\triangle}$	115.3 ±1.4$^{**\triangle\triangle}$	2.37 ±0.03$^{***\triangle\triangle\triangle}$	244.2 ±1.7$^{***\triangle\triangle\triangle}$

K-H solution was used as control, intrasinus pressure of isolated carotid sinus was fixed at 100 mmHg for 20 min as the control, measured the functional parameters of baroreceptor, then K-H solution containing resveratrol (60 μmol· L^{-1}) perfusing for 50 min, after washing out resveratrol with K-H solution, *L*-NAME (100 μmol· L^{-1}), Bay K8644 (500 nmol· L^{-1}) and sodium orthovanadate (1 mmol· L^{-1}) perfusing for 15 min, respectively. Then in the presence of the drugs, resveratrol (60 μmol· L^{-1}) perfusing for another 50 min. The parameters were measured respectively. $n = 6$, $\bar{x} \pm s$. $^{+}P > 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ *vs* control; $^{##}P < 0.01$, $^{###}P < 0.001$ *vs* resveratrol (60 μmol· L^{-1}) group; $^{\triangle\triangle}P < 0.01$, $^{\triangle\triangle\triangle}P < 0.001$ *vs* sodium orthovanadate (1 mmol· L^{-1}) group

L^{-1}) on FCCB. Sodium orthovanadate (1 mmol· L^{-1}) did not affect FCCB ($P > 0.05$) and did not influence the effects of resveratrol (60 μmol· L^{-1}) either. Shown in Table 2.

Discussion

The present study is the first time to show that resveratrol inhibited CBA in a concentration-dependent manner. By perfusing the left isolated carotid sinus baroreceptor of the rats with resveratrol, the FCCB was shifted to the right and downward with decrease in PS and increase in TP, indicating the inhibitory effect of resveratrol on CBA.

It has been reported that NOS is present in endothelial cells and in sensory nerves innervating the carotid sinus region and administration of nitric oxide

(NO) or NO donors to isolated carotid sinus inhibits the activity of baroreceptor[13]. Chapleau et al[14] showed that in the isolated carotid sinus, the placement of activated bovine aortic endothelial cells decreased baroreceptor activity (BRA) in a reversible manner. NO could suppress BRA. Moreover, increasing evidences have indicated that NO could act as an autocrine regulator of sodium current in baroreflex neurons, therefore suppressed action potential discharge of baroreceptor[15], and stimulated calcium-dependent potassium channel on baroreceptor[16]. The activation of potassium channel could hyperpolarize baroreceptor neurons, then inhibit baroreflex[17]. Furthermore, available data have demonstrated that resveratrol could stimulate eNOS expression, thus subsequent NO release from endothelium cells[18,19] and also could produce endothelium-dependent and nitric oxide-mediated vasodilation in human internal mammary artery[20] and rat thoracic aorta[21]. In present experiment, pretreatment with *L*-NAME, non-selective NOS inhibitor, completely blocked the effect of resveratrol on CBA. Based on the above observation, it is conceivable that the local released NO induced by resveratrol from carotid sinus region may contribute to the effect of resveratrol on CBA.

Evidence has been present to show that the primary mechanism of activation of baroreceptors was mechanical deformation during vascular stretch[22]. The deformation would non-selectively activate cation ion currents on the membrane of neurons. Moreover, it has been demonstrated that stretching of the wall of carotid sinus may induce an increase in calcium influx on baroreceptor neurons which is mediated by stretch-activated channels[23]. Also resveratrol might have Ca^{2+} antagonistic properties and could inhibit extracellular Ca^{2+} influx and Ca^{2+} release from intracellular stores[10]. Our present study showed that L-type calcium channel opener Bay K8644 abrogated the effect of resveratrol, thus the inhibitory effect of resveratrol on CBA could be ascribed to the decreased calcium influx.

Resveratrol possesses comparable protein tyrosine kinase inhibitory activity[24]. Tyrosine kinase is considered as an important modulator of vascular smooth muscle[25]. Furthermore, the inhibitor of tyrosine phosphorylation, sodium orthovanadate could decrease tyrosine phosphorylation and resulted in the contraction of vascular smooth muscle[26,27]. In this study, sodium orthovanadate did not influence the inhibitory effect of resveratrol, it may be concluded that protein tyrosine kinase pathway was not involved in the action of resveratrol on CBA.

Epidemiologic studies have demonstrated that the incidence of coronary artery disease in France is strinkingly lower as compared with that in other western countries with a fat-containing diet. This so-called "French paradox" has been attributed to moderate consumption of red wine in France. Resveratrol has been designated as the responsible agent of the French paradox[28], which indicates its cardiovascular benefit effect. Cardiovascular disease is the leading cause of mortality in postmenopausal women. As a kind of phytoestrogen, resveratrol may play an important role in hormone replacement therapy and thus reduce the risk of cardiovascular disease in postmenopausal women. It is known that the short-term modulation of blood pressure is contributed to the activity of arterial baroreceptor. In our study, resveratrol demonstrates inhibitory effects on CBA, which might be expected to weaken the ability to antagonize hypertension and destabilize blood pressure. More experiments should be done to test the safety of resveratrol as an alternative medicine in clinical treatment of cardiovascular disease.

In summary, resveratrol inhibits the carotid sinus baroreceptor activity, which may be mediated by the locally released NO and decreased calcium influx.

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