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MODULATION OF SIRT1 ACTIVITY IN ENDOTHELIAL CELLS AFFECTS THE THERAPEUTIC EFFECTS OF RESVERATROL IN APOLIPOPROTEIN E DEFICIENT MICE

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Introduction: Sirtuin-1 (SIRT1) possesses anti-metabolic and vascular aging properties, and elicits protective functions against atherosclerosis and metabolic abnormalities. Resveratrol, one of the activator of SIRT1, performs therapeutic effects on cardiovascular and metabolic homeostasis through SIRT1-dependent and SIRT1-independent pathway. The present study aimed to investigate the therapeutic effects of resveratrol in hypercholesterolemic apolipoprotein E-deficient (ApoE^{-/-}) mice with different endothelial SIRT1 expression and activity levels.

Method: ApoE^{-/-} mice with endothelial-selective overexpression of wild type human SIRT1 (hSIRT1) (WIS ApoE^{-/-}) or its dominant negative mutant hSIRT1 (H363Y) (HIS ApoE^{-/-}) under high fat high cholesterol diet were administered with resveratrol for eight weeks. Serum and tissues were collected for lipid profiling and histological analysis. SIRT1 activity was evaluated by western blot analysis and in-vitro deacetylation assay.

Results: Resveratrol significantly improved serum and liver lipid profiles and attenuated atherosclerotic lesions in both ApoE^{-/-} and HIS ApoE^{-/-} mice. However, it adversely affected serum and liver lipid profiles in WIS ApoE^{-/-} mice. Resveratrol did not significantly affect SIRT1 activity in liver tissues of all mice groups.

Conclusion: The protected effects on cardiovascular and metabolic homeostasis of resveratrol in ApoE^{-/-} mice were modulated by SIRT1 activity in endothelial cells.

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VASODILATORY EFFECT OF NARIRUTIN IN RAT MESENTERIC ARTERIES AND AORTAE

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Introduction: Narirutin, a kind of flavanones, is abundant in citrus fruits. It has been shown to possess anti-inflammatory and anti-oxidative effects. Its structural similarities, naringin and naringenin, were found to be vasoprotective. However, the vasoprotective effect of narirutin has not yet been reported. This study aimed to investigate the vasodilatory effect of narirutin.

Method: Male Sprague-Dawley (SD) rats (8-10 weeks old), spontaneously hypertensive rats (SHR) (36-40 weeks old) and the normotensive controls (Wistar-Kyoto rats; WKY) were used in this study. The mesenteric arteries and aortae were isolated for the measurement of isometric tension in relaxation and contraction studies, respectively.

Results: The results showed that narirutin caused a concentration-dependent dilation of mesenteric arteries in SD rats. The vasodilation was stronger when the endothelium was present and this effect was partially blocked by L-NAME (a nitric oxide synthase inhibitor), ODQ (a soluble guanylyl cyclase inhibitor) or 4-aminopyridine (a voltage-activated K⁺ channel blocker). Besides, the impaired acetylcholine (Ach) induced-dilation of mesenteric arteries in SHR was restored when the arteries were pre-incubated with narirutin (10 μ M and 30 μ M) for 30 minutes. This effect was not observed in the mesenteric arteries of WKY. Furthermore, the Ach-induced endothelium-dependent contraction was studied in the aorta of SHR in the presence of L-NAME. The Ach-induced vasocontraction in SHR was decreased and even abolished when the aortae were pre-incubated with 10 μ M and 30 μ M of narirutin, respectively.

Conclusion: This study demonstrated that the direct vasodilation induced by narirutin was partially endothelium-dependent, which may involve the participation of nitric oxide and voltage-activated K⁺ channels. Besides, narirutin was able to restore the impaired endothelium-dependent vasodilation and augmented endothelium-dependent vasocontraction in hypertensive rat model.