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Impaired Transient Receptor Potential Vanilloid 4-Mediated Dilation of Mesenteric Arteries in Spontaneously Hypertensive Rats

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Abstract : Background: Hypertension is increasingly becoming a matter of medical and public health importance. The maintenance of normal blood pressure requires a balance between cardiac output and total peripheral resistance. The endothelium, through the release of vasodilating factors, plays an important role in the control of total peripheral resistance and hence blood pressure homeostasis. Transient Receptor Potential Vanilloid type 4 (TRPV4) is a mechanosensitive non-selective cation channel that is expressed on the endothelium and contributes to endothelium-mediated vasodilation. So far, no data are available about the morphological and functional status of this channel in hypertensive cases. Objectives: This study aimed to investigate whether there is any difference in the morphological and functional features of TRPV4 in the mesenteric artery of normotensive and hypertensive rats. Methods: Functional feature of TRPV4 in four experimental animal groups: young and adult Wistar-Kyoto rats (WKY-Y and WKY-A), young and adult spontaneously hypertensive rats (SHR-Y and SHR-A), was studied by adding 5 µM 4αPDD (TRPV4 agonist) to mesenteric arteries mounted in a four-chamber wire myograph and pre-contracted with 4 µM phenylephrine. The 4αPDD-induced response was investigated in the presence and absence of 1 µM HC067047 (TRPV4 antagonist), 100 µM L-NAME (nitric oxide synthase inhibitor), and endothelium. The morphological distribution of TRPV4 in the wall of rat mesenteric arteries was investigated by immunostaining. Real-time PCR was used in order to investigate mRNA expression level of TRPV4 in the mesenteric arteries of the four groups. The collected data were expressed as mean ± S.E.M. with n equal to the number of animals used (one vessel was taken from each rat). To determine the level of significance, statistical comparisons were performed using the student's t-test and considered to be significantly different at $p<0.05$. Results: 4αPDD induced a relaxation response in the mesenteric arterial preparations (WKY-Y: 85.98% ± 4.18; n = 5) that was markedly inhibited by HC067047 (18.30% ± 2.86; n= 5; $p<0.05$), endothelium removal (19.93% ± 1.50; n = 5; $p<0.05$) and L-NAME (28.18% ± 3.09; n = 5; $p<0.05$). The 4αPDD-induced relaxation was significantly lower in SHR-Y compared to WKY-Y (SHR-Y: 70.96% ± 3.65; n = 6, WKY-Y: 85.98% ± 4.18; n = 5-6, $p<0.05$. Moreover, the 4αPDD-induced response was significantly lower in WKY-A than WKY-Y (WKY-A: 75.58 ± 1.30; n = 5, WKY-Y: 85.98% ± 4.18; n = 5, $p<0.05$). Immunostaining study showed immunofluorescent signal confined to the endothelial layer of the mesenteric arteries. The expression of TRPV4 mRNA in SHR-Y was significantly lower than in WKY-Y (SHR-Y; 0.67RU ± 0.34; n = 4, WKY-Y: 2.34RU ± 0.15; n = 4, $p<0.05$). Furthermore, TRPV4 mRNA expression in WKY-A was lower than its expression in WKY-Y (WKY-A: 0.62RU ± 0.37; n = 4, WKY-Y: 2.34RU ± 0.15; n = 4, $p<0.05$). Conclusion: Stimulation of TRPV4, which is expressed on the endothelium of rat mesenteric artery, triggers an endothelium-mediated relaxation response that markedly decreases with hypertension and growing up changes due to downregulation of TRPV4 expression.

Keywords : hypertension, endothelium, mesenteric artery, TRPV4
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