Angiotensin-(1-9) prevents vascular remodeling by decreasing vascular smooth muscle cell dedifferentiation through a FoxO1-dependent mechanism

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Abstract

The renin-angiotensin system, one of the main regulators of vascular function, controls vasoconstriction, inflammation and vascular remodeling. Antagonistic actions of the counter-regulatory renin-angiotensin system, which include vasodilation, anti-proliferative, anti-inflammatory and anti-remodeling effects, have also been described. However, little is known about the direct effects of angiotensin-(1-9), a peptide of the counter-regulatory renin-angiotensin system, on vascular smooth muscle cells. Here, we studied the anti-vascular remodeling effects of angiotensin-(1-9), with special focus on the control of vascular smooth muscle cell phenotype. Angiotensin-(1-9) decreased blood pressure and aorta media thickness in spontaneously hypertensive rats. Reduction of media thickness was associated with decreased vascular smooth muscle cell proliferation. In the A7r5 VSMC cell line and in primary cultures of rat aorta smooth muscle cells, angiotensin-(1-9) did not modify basal proliferation. However, angiotensin-(1-9) inhibited proliferation, migration and contractile protein decrease induced by platelet derived growth factor-BB. Moreover, angiotensin-(1-9) reduced Akt and FoxO1 phosphorylation at 30 min, followed by an increase of total FoxO1 protein content. Angiotensin-(1-9) effects were blocked by the AT2R antagonist PD123319, Akt-Myr overexpression and FoxO1 siRNA. These data suggest that angiotensin-(1-9) inhibits vascular smooth muscle cell dedifferentiation by an AT2R/Akt/FoxO1-dependent mechanism.

Palabras clave

Palabras clave de autor: Angiotensin-(1-9); AT2R; Cell dedifferentiation; FoxO1; Platelet derived growth factor; Spontaneously hypertensive rat; Vascular smooth muscle cell

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