



Sonic Hedgehog Carried by Microparticles Corrects Angiotensin II-Induced Hypertension and Endothelial Dysfunction in Mice

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Résumé en anglais

Microparticles are small fragments of the plasma membrane generated after cell stimulation. We recently showed that Sonic hedgehog (Shh) is present in microparticles generated from activated/apoptotic human T lymphocytes and corrects endothelial injury through nitric oxide (NO) release. This study investigates whether microparticles bearing Shh correct angiotensin II-induced hypertension and endothelial dysfunction in mice. Male Swiss mice were implanted with osmotic minipumps delivering angiotensin II (0.5 mg/kg/day) or NaCl (0.9%). Systolic blood pressure and heart rate were measured daily during 21 days. After 7 day of minipump implantation, mice received i.v. injections of microparticles (10 µg/ml) or i.p. Shh receptor antagonist cyclopamine (10 mg/kg/2 days) during one week. Angiotensin II induced a significant rise in systolic blood pressure without affecting heart rate. Microparticles reversed angiotensin II-induced hypertension, and cyclopamine prevented the effects of microparticles. Microparticles completely corrected the impairment of acetylcholine- and flow-induced relaxation in vessels from angiotensin II-infused mice. The improvement of endothelial function induced by microparticles was completely prevented by cyclopamine treatment. Moreover, microparticles alone did not modify NO and O₂·⁻ production in aorta, but significantly increased NO and reduced O₂·⁻ productions in aorta from angiotensin II-treated mice, and these effects were blocked by cyclopamine. Altogether, these results show that microparticles bearing Shh correct angiotensin II-induced hypertension and endothelial dysfunction in aorta through a mechanism associated with Shh-induced NO production and reduction of oxidative stress. These microparticles may represent a new therapeutic approach in cardiovascular diseases associated with decreased NO production.

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