Sonic hedgehog carried by microparticles prevents angiotensin II-induced hypertension and endothelial dysfunction in mice

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Résumé en anglais	Microparticles (MPs) are small fragments generated from the plasma membrane after cell stimulation. Among the candidate proteins harbored by MPs, we recently showed that morphogen Sonic hedgehog is present in MPs generated from activated/apoptotic human T lymphocytes and corrects endothelial injury through nitric oxide (NO) release (Agouni et al. FASEB J 2007). The present study further investigates whether MPs bearing Shh prevent angiotensin II (Ang II)-induced hypertension and endothelial dysfunction in mice. Male Swiss mice (6–8 week old) were subcutaneously implanted with osmotic minipumps delivering Ang II (0.5 mg/kg per day) or NaCl (0.9%, control group). Systolic blood pressure and heart rate were measured daily during 21 consecutive days using tail cuff plethysmography connected to a computerized system (LE 5002 # , BIOSEB). Mice were tained for 7 days. After 7 day of minipump implantation, mice received i.v. injections of MPs (10 µg/mL) or i.p. Sonic Hedgehog receptor antagonist cyclopamine (10 mg/kg per 2 days) during 1 week prior sacrifice. Thoracic aorta was removed, cleaned of connective tissue and cut in rings (3 mm length) and mounted in a myograph to study vascular reactivity. Ang II induced a significant rise in systolic blood pressure without affecting heart rate when compared to control mice. Interestingly, MPs alone did not modify both parameters but reversed Ang II-induced hypertension. Moreover, cyclopamine prevented the effects of MPs on Ang II-induced hypertension, suggesting the involvement of a Sonic Hedgehog-dependent mechanism. In the aorta, MPs alone slightly increased the sensitivity of endothelium-dependent relaxation to acetylcholine and completely reversed the impairment of acetylcholine-induced relaxation in aorta from Ang II-infused mice. The improvement of endothelial function induced by MPs was completely prevented by cyclopamine treatment. Moreover, measurement of NO production showed that MPs alone did not modify NO production in aorta, but significantly restored its decrease in Ang II-treated mice. Altogether, these results show that MPs bearing Sonic hedgehog prevent Ang II-induced hypertension and endothelial dysfunction in aorta through a mechanism associated with Sonic hedgehog-induced NO production. These MPs may represent a new therapeutic approach in cardiovascular diseases associated with decreased NO production.
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