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Effect of Losartan on the Angiotensin II-Mediated Secretion of tPA and PAI-1 by Human Vascular Smooth Muscle Cells

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AIM

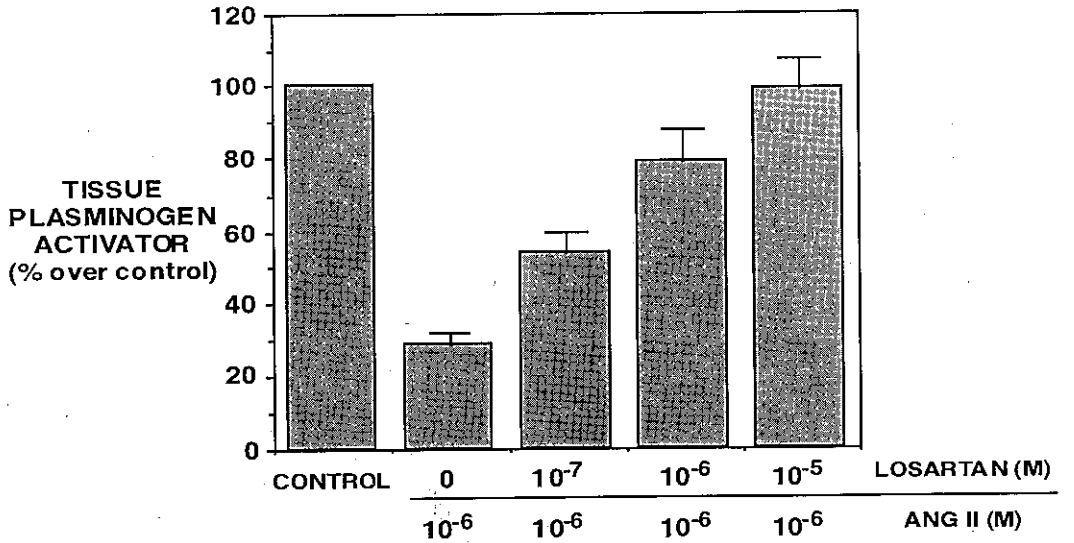
The pathogenesis of thromboembolic complications, such as ischemic stroke and myocardial infarction, is crucially determined by the fibrinolytic system, which in turn is controlled by several mechanisms, such as the balance between tissue-type plasminogen activator (tPA) and its primary inhibitor, plasminogen activator inhibitor-1 (PAI-1). Thromboembolic complications are significantly more frequent in patients with arterial hypertension. Angiotensin II (Ang II) is an endogenous vasoactive peptide involved in the regulation of blood pressure and has been implicated in atherogenic and restenotic processes. The aim of this study was to investigate the effect of the antihypertensive agent losartan, an Ang II type 1 receptor antagonist, on Ang II-mediated secretion of tPA and PAI-1 by primary human vascular smooth muscle cells (VSMC).

METHODS

VSMC were established from pulmonary arteries obtained from patients undergoing lobectomy for peripheral lung cancer and characterized by immunohistochemical staining using monoclonal antibodies. Subconfluent cell cultures were serum-deprived (0.1% FCS) for 48 h and were then pretreated with losartan (10^{-7}-10^{-5} M) or 0.1% FCS alone for 15 min, followed by the addition of Ang II (10^{-9}-10^{-6} M) or 0.1% FCS alone. In all cases, cells were cultured for further 24 h. At the end of the incubation period the supernatant was removed and assayed for tPA and PAI-1, using ELISA.

RESULTS

We found that PAI-1 was not significantly affected by Ang II. However, Ang II decreased tPA secretion by VSMC in a dose dependent manner, an effect that became satistically significant at concentrations of 10^{-7} M and higher. Losartan reversed this effect of Ang II in a dose dependent manner. We also observed that losartan alone increased the secretion of tPA and decreased the secretion of PAI-1 by VSMC, in a dose dependent manner, by a mechansim that remains to be clarified.



Effect of Losartan on the ANG II-mediated tPA secretion by human VSMC

CONCLUSIONS

The above described effects of losartan on Ang II-mediated secretion of tPA may be beneficial in preventing thrombus formation in patients treated for hypertension or ischemic heart disease.