6. Abstract

Objective. Apoptosis of VSMC is considered as a crucial event in the pathogenesis of vascular diseases like aneurysms. In this study, we tested the hypothesis that high-molecular-weight kininogen is directly involved in cellular pathways by preventing apoptosis of VSMC.

Methods and results. In VSMC derived from BN/Ka, a rat strain which is plasma-deficient in HMWK due to a mutation of the kininogen gene, basal mRNA levels of apoptotic proteins were elevated and of the anti-apoptotic Bcl-X_L were decreased compared to BN rats. HMWK concentration-dependently prevented aortic VSMC from entering apoptosis which was associated with a down-regulation of apoptotic index, cleaved caspase 3 and 9, decreased caspase 8 activity and reduced release of cytochrome C and cathepsin B into the cytosol. Consistent with these results, the expression of the anti-apoptotic protein Bcl-X_L and phospho-42/44 MAPK was increased by HMWK. These findings were confirmed by rescue of VSMC transfected with an HMWK expression vector. All observed effects of HMWK were independent of bradykinin. No endogeneous HMWK mRNA production was detectable in VSMC. Furthermore, VSMC were able to bind and internalize irreversibly HMWK, which colocalized with active apoptotic proteases.

Conclusion. Our findings, demonstrating for the first time multiple direct anti-apoptotic effects of HMWK in VSMC, point to a cellular mechanism by which HMWK rescues VSMC from apoptosis.