## S28-6 Role of bradykinin in the angiotensin II type 2 receptor-mediated vasodilatation

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Among many factors inducing vascular lesions associated with atherosclerosis, hypertension and diabetes, angiotensin II (Ang II) has been recognized as a major factor behind endothelial dysfunction and atherosclerotic plaque development; stimulation of the vascular Ang II type 1 ($AT_1$) receptor produces vasoconstriction and proinflammatory responses. In contrast to these effects mediated by the $AT_1$ receptor, Ang II exerts vasodilatation and anti-inflammatory activities by stimulating the $AT_2$ receptor. We have demonstrated that bradykinin (BK) and its receptors play an important role in the $AT_2$ receptor-dependent activation of endothelial nitric oxide synthase. BK is generated and liberated from aortic segments of rat and mouse in vitro in response to Ang II ($>10^{-9}$ M) via the $AT_2$ receptor. The $AT_2$-receptor-dependent BK generation by aorta is enhanced by ARBs and abolished by a serine-proteinase inhibitor and endothelial denudation, suggesting the $AT_1$-receptor-repressive, serine-proteinase-involved and endothelial-dependent mechanisms. Ang-(1-7) ($>10^{-10}$ M), a vasodilator peptide generated from Ang II by ACE2, also reveals the activity stimulating BK generation in aorta via the activation of $AT_2$ receptor. These results suggest that both Ang II and Ang-(1-7) antagonize the $AT_1$-receptor-mediated vasoconstrictor effect by stimulating BK generation via the $AT_2$ receptor. Masking the $AT_1$ receptor-mediated suppression of $AT_2$ receptor signaling associated with vascular BK generation seems to be one of the mechanisms underlying the activation of $AT_2$ receptor by ARBs