Purinergic P2Y(6) receptors heterodimerize with angiotensin AT1 receptors to promote angiotensin II-induced hypertension

Abstract

The angiotensin (Ang) type 1 receptor (AT1R) promotes functional and structural integrity of the arterial wall to contribute to vascular homeostasis, but this receptor also promotes hypertension. In our investigation of how Ang II signals are converted by the AT1R from physiological to pathological outputs, we found that the purinergic $P2Y_6$ receptor ($P2Y_6R$), an inflammation-inducible G protein (heterotrimeric guanine nucleotide–binding protein)–coupled receptor (GPCR), promoted Ang II–induced hypertension in mice. In mice, deletion of $P2Y_6R$ attenuated Ang II–induced increase in blood pressure, vascular remodeling, oxidative stress, and endothelial dysfunction. AT1R and $P2Y_6R$ formed stable heterodimers, which enhanced G protein–dependent vascular hypertrophy but reduced β-arrestin–dependent AT1R internalization. Pharmacological disruption of AT1R-$P2Y_6R$ heterodimers by the $P2Y_6R$ antagonist MRS2578 suppressed Ang II–induced hypertension in mice. Furthermore, $P2Y_6R$ abundance increased with age in vascular smooth muscle cells. The increased abundance of $P2Y_6R$ converted AT1R-stimulated signaling in vascular smooth muscle cells from β-arrestin–dependent proliferation to G protein–dependent hypertrophy. These results suggest that increased formation of AT1R-$P2Y_6R$ heterodimers with age may increase the likelihood of hypertension induced by Ang II.