Public Abstract
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Title:CONTRIBUTION OF AT1R MECHANOACTIVATION TO THE ARTERIAL MYOGENIC RESPONSE AND ITS REGULATION BY RGS5 PROTEIN IN SKELETAL MUSCLE ARTERIOLES

The circulatory system consists of large (e.g. aorta) and small (e.g. arterioles) blood vessels. Blood vessels are not merely a system of rigid tubes but are able to increase or decrease their diameter as required. The small blood vessels are more responsive to alterations in blood pressure. An increase or decrease in blood pressure induces constriction or dilation of the small vessels, respectively. This is called “myogenic response” and is necessary for regulating blood pressure and flow, particularly at the local tissue level. Much has been elucidated with respect to cellular signaling cascades for the myogenic response, whereas less has been known regarding a fundamental question: how are mechanical stimuli (e.g. blood pressure) detected and, in turn, how are well-defined signaling processes initiated in the myogenic response. Growing evidence supports the angiotensin II type 1 receptor (AT1R) serving as a novel mechanosensor and contributing to myogenic vasoconstriction of diverse vascular beds. However, the exact downstream signaling pathways of AT1R mechanoactivation that contribute to pressure-induced vasoconstriction are yet to be completely delineated. We found that mechanically activated AT1R may generate a specific downstream molecule, diacylglycerol, and in turn activate a regulatory protein, PKC, that presumably induces actin cytoskeleton reorganization for the myogenic constriction. In addition, appropriate control of blood flow is critical to meet the metabolic demands of tissues (e.g. pumping of cardiac muscle or brain activity). Conversely, an impaired myogenic response can cause diverse pathophysiological results. For example, insufficient blood flow due to excessive myogenic constriction provokes cardiac or brain ischemia, cerebral vasospasm, or stroke. However, despite its physiological and clinical significance, mechanisms underlying the regulation of AT1R-mediated myogenic response are incompletely understood. In regard to this, small arteries likely exhibit negative feedback regulatory mechanisms to prevent an exaggerated myogenic response. We tested the general hypothesis that pressure-dependent vasoconstriction is modulated by mechanisms underlying negative regulation of AT1R signaling. Specifically, RGS (Regulators of G-protein Signaling) proteins are viewed as important regulatory molecules for limiting myogenic vasoconstriction. It was found in this study that ligand-dependent or independent activation of the AT1R causes trafficking of RGS5 protein, which may precisely modulate Ang II or myogenic-mediated constriction by terminating Gq/11 protein-dependent downstream signaling. This study will contribute to identification of the novel mechanisms underlying myogenic responsiveness and potential therapeutic targets for pharmacological drug discovery that can directly impact hemodynamics in the heart, brain, or other organs.