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Novel molecular mechanism for sympathetically mediated hypertension triggered by alpha1a-adrenoceptor genetic variant

Anush Oganesian

University of Washington, USA

Abstract

Various cardiovascular disorders, such as hypertension and heart failure, are associated with polymorphisms in genes involved in the regulation of adrenergic system, mostly beta-Adrenergic Receptors (AR) and alpha2ARs. Three alpha1AR (α_1AR) subtypes have been characterized and are expressed in human heart and vessels (α_{1a}, α_{1b}, α_{1d}), mediating actions of the sympathetic nervous system through binding of the endogenous catecholamines epinephrine and norepinephrine. The predominant subtype in human vessels and heart is α_{1a}AR. A few studies have reported an association between α_{1a}AR polymorphisms with hypertension and heart failure in humans. Previously 9 naturally occurring human SNPs in the α_{1a}AR coding region have been identified and pharmacologically characterized. The α_{1a}AR-G247R (α_{1a}-247R) SNP present in the third intracellular loop of the α_{1a}AR was identified in a patient with severe hypertension. Several reports also suggest that specific α_{1a}AR genetic variants are associated with human hypertension. We therefore explored whether there are unique molecular mechanisms that might account for this association. We recently reported that α_{1a}-247R confers proliferative advantage to fibroblasts cultured under serum-deprived conditions and importantly, in the absence of agonist stimulation. Our results suggest that increased cell proliferation triggered by the naturally occurring human genetic variant α_{1a}AR-G247R is due to intrinsic MMP-7 and ADAM-12 dependent activation of an autocrine loop leading to constitutive production of HB-EGF and transactivation of EGFR in the absence of agonist. These findings provide the first evidence for a novel mechanism of sympathetically-mediated human hypertension triggered by a naturally occurring human genetic variant, α_{1a}-247R activated signal transduction pathway. We also study the constitutive and agonist-induced biological effects of this SNP and the signaling pathways activated in cardiomyoblasts. We show that cardiomyoblasts expressing α_{1a}-247R exhibit increased proliferation without agonist stimulation, undergo hypertrophy upon agonist stimulation, and change the cell morphology and phenotype to highly proliferative, fibroblast-like cells. These data confirm our previous findings that agonist- and serum-independent EGFR transactivation leading to enhanced proliferation of fibroblasts expressing α_{1a}-247R is not cell type dependent but generalizable phenomena. Our observations also suggest that this SNP may lead to changes of vessel and heart structure, and lead to cardiovascular disease. These findings also raise the tantalizing hypothesis that a naturally occurring α_{1a}AR genetic variant may be mechanistically involved in some forms of human hypertension, and that MMP/ADAM-specific inhibitors may be effective therapeutic agents for treatment of some forms of sympathetically-mediated human hypertension.

Biography

Anush Oganesian is a Research Assistant Professor in the Department of Anesthesiology at the University of Washington. She received her BS/MS in Molecular Biology/Chemistry from the Yerevan University in Armenia and her PhD in Biochemistry/Organic Chemistry from the Institute of Element Organic Compounds, Academy of Sciences in Moscow, Russia. Anush did her post-doctorial training at the University of Washington with Linda Sandell in the Department of Orthopedics studying the extracellular matrix proteins including the N-propeptide of type IIA procollagen and its interaction with TGFß1 and BMP-2 proteins. She continued her postdoctoral training in the laboratory of Daniel Bowen-Pope in the Department of Pathology focusing on biochemical characterization, functional studies and signal transduction pathways regulated by PTPRQ and Phogrin, novel transmembrane protein tyrosine phosphatases with PTEN-like lipid-phosphatase activities.