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An old argument with a new paradigm

Thomas Thekkumkara
Texas Tech University, USA

Cardiovascular disease (CVD) is the leading cause of death in the U.S. for both men and women. Angiotensin II, through angiotensin type 1 receptor (AT1R), has a significant effect on cardiovascular dysfunction, making it a target for therapeutic intervention. Endogenous estrogen protects premenstrual women from cardiovascular disease; however, multiple clinical studies suggest otherwise. 2-methoxyestradiol (2ME2), a natural nontoxic metabolite of estrogen, has shown no significant physiological responses due to its low concentration and short half-life in circulation. Ongoing studies in our laboratory are focused on determining the pharmacological effect of 2ME2 on AT1R gene expression. In recent studies we examined the effects of 2ME2 on rat epithelial and vascular smooth muscle cells exposed for 24 hours and showed MAP Kinase mediated down-regulation of AT1R gene expression. 2ME2 was found to bind with high affinity to an endoplasmic reticulum membrane bound G-protein coupled receptor (GPR30) independent of classical nuclear estrogen receptors. GPR30 activation subsequently led to MAP Kinase activation through transactivation of an EGFR mediated pathway. This study provides the first evidence that 2ME2 is capable of altering AT1R gene expression. Furthermore, 2ME2 mediated down-regulatory effect on AT1R was correlated with reduced mean arterial blood pressure in spontaneously hypertensive rats. Because AT1R has a critical role in the control of CVD, 2ME2- induced changes in receptor expression may provide beneficial effects to the cardiovascular and other systems. This will further provide an indirect explanation for the premenopausal beneficial effects of estrogen.

Biography

Thomas Thekkumkara has completed his PhD at the age of 30 years from Kanpur University and postdoctoral studies from Case Western Reserve University School of Medicine in Cleveland Ohio. He is a Professor of Biomedical Sciences and the Regional Dean of the Texas Tech University Health Sciences Center School of Pharmacy. He has published more than 50 manuscripts in journals of high impact and stature. This body of work is widely recognized by the scientific community as evidenced by more than 1450 citations of his published work, his collaborations with national and international scientists, and membership in major scientific societies.

Thomas.Thekkumkara@ttuhsc.edu