**DISTINCT ROLES OF CALCIUM & CYCLIC AMP IN ANGIOTENSIN II-INDUCED EXPRESSION OF EARLY GROWTH RESPONSE FACTOR-1 (EGR-1) IN VASCULAR SMOOTH MUSCLE CELLS**

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Angiotensin-II (Ang-II) is a key vasoactive peptide that has been implicated in the pathogenesis of vascular diseases. Ang-II elevates intracellular Ca2+ through activation of the store-operated calcium entry (SOCE) involving an inositol-3-phosphate receptor (IP3R)-coupled depletion of endoplasmic reticular Ca2+ and a subsequent activation of the stromal interaction molecule 1 (STIM-1) /Orai-1 complex. Ang-II has also been shown to modulate adenylyl cyclase/cAMP signaling system. We recently reported that Ang-II induces the expression of Egr-1, a zinc finger transcription factor that regulates the transcription of multiple genes implicated in the pathogenesis of vascular diseases such as atherosclerosis. In the present studies, we have examined the contributions of SOCE and cAMP in mediating Ang-II-induced Egr-1 expression and associated signaling in VSMC. Pharmacological blockade SOCE by 2-aminoethoxydiphenyl borate (2-APB) decreased Ang-II-induced Ca2+ release and attenuated Ang-II-induced enhanced expression of Egr-1 protein and mRNA levels. Furthermore, siRNA mediated silencing of STIM-1 or Orai-1 attenuated Ang-II-induced Egr-1 expression as well as ERK1/2and CREB phosphorylation. In addition, elevation of cAMP either by Isoproterenol (ISO), a β-receptor agonist or forskolin (FSK), a non-receptor activator of adenylate cyclase, attenuated Ang-II-induced Egr-1 expression which was accompanied by an increase in phosphorylation of the vasodilator-activated phosphoprotein (VASP), a substrate of protein kinase A (PKA), and a decrease in ERK phosphorylation. Furthermore, blockade of PKA using H89 decreased VASP phosphorylation, restored Ang-II-induced ERK phosphorylation and abolished ISO- and FSK-mediated inhibition of Ang-II-induced Egr-1 expression. In summary, these results suggest that SOCE-induced increase in calcium is essential to induce Egr-1 expression in response to Ang-II whereas stimulation of cAMP/PKA pathway antagonizes the effect of Ang-II on Egr-1 expression. (Supported by grants from CIHR).