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Oral presentation

cGMP effects on vascular tone: modulating the activity of myosin light chain phosphatase

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Background

During flow-mediated vasodilatation, nitric oxide activates guanylate cyclase and the resultant increase cGMP leads to an activation of PKGI. PKGI activates a number of targets in the smooth muscle cell that result in smooth muscle relaxation, including MLC phosphatase. MLC phosphatase isolated from smooth muscle is a holoenzyme consisting of three subunits; a 20 kDa subunit, a 38 kDa catalytic subunit and a myosin targeting subunit (MYPT1). MYPT1 has two isoforms that differ by the presence of a an alternatively spliced 31 bp 3' exon; exon inclusion codes for a MYPT1 that lacks a COOH-terminus leucine zipper (LZ-), while exon exclusion shifts the reading frame and codes for a LZ+ MYPT1 isoform.

Results

We have demonstrated that PKGI mediated activation of the MLC phosphatase requires the expression of a LZ+ MYPT1, and the relative expression of LZ+/LZ- MYPT1 isoforms determines the sensitivity to cGMP mediated smooth muscle relaxation. We have also demonstrated that in animal models of heart failure (CHF), LZ+ MYPT1 expression and the sensitivity to cGMP mediated smooth muscle relaxation both decline. Further, activation of p42/44 MAPK, but not p38 MAPK, signaling occurs during CHF, and treatment with angiotensin receptor antagonists prevents the activation of p42/44 MAPK and preserves both normal LZ+ MYPT1 expression and normal sensitivity to cGMP mediated smooth muscle relaxation.

Conclusion

These results suggest that an AT1 receptor mediated activation of the p42/44 MAPK signaling pathway could regulate alternative splicing of the LZ MYPT1 transcript to produce LZ+/LZ- MYPT1 isoforms. Further, a number of investigators have demonstrated that a decrease in LZ+ MYPT1 expression is associated with heart failure, portal hypertension and pre-eclampsia, and thus, LZ MYPT1 expression could be a marker for vascular disease.